

cancer); however, these studies were based on small numbers of tumors (Huang *et al.* 1999, Laurent-Puig *et al.* 2001, Ueta *et al.* 2002).

Properties

HCV is an enveloped RNA virus, which causes most non-B viral hepatitis that is transmitted parenterally (i.e., by injection, transfusion, or other contact with body fluids). It is a member of the *Flaviviridae* family of viruses and has a particle size of about 50 nm in diameter (He *et al.* 1987). The positive-sense RNA genome (9,600 nucleotides) codes for production of a polyprotein (3,000 amino acids); enzymes produced by the virus and the host cell then cleave the polyprotein into the smaller structural and nonstructural proteins that make up the mature virus particle. The structural proteins, which are incorporated into the viral envelope, consist of the core (nucleocapsid) protein and two glycoproteins (E1 and E2). The nonstructural proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) serve as enzymes essential for protein processing and RNA replication; their functions include protease, nucleotide triphosphatase, RNA helicase, and RNA polymerase activity (Rosenberg 2001).

Replication of HCV often results in random mutations that are not corrected by the RNA polymerase because it lacks a proofreading function. As a result, the genomes of HCV strains show extensive variability. However, some regions of the genome are more variable than others, and classification of HCV genotypes is based on differences in the less variable regions of the genome. HCVs can be divided into six phylogenetically distinct groups designated as clades (groups of genotypes that share a common ancestor). Within the clades, a number of subtypes (individual genotypes) have been defined (Simmonds *et al.* 1993, Bukh *et al.* 1995, Simmonds 1995, Robertson *et al.* 1998). All known types of HCV have the potential to cause serious liver disease.

Infection, Prevention, and Treatment

HCV can cause acute or chronic hepatitis. Acute hepatitis C usually is characterized by elevated or fluctuating levels of alanine transaminase (ALT). People with acute hepatitis C either have no symptoms (60% to 70%) or have mild clinical disease symptoms: 10% to 20% have nonspecific symptoms, such as nausea, vomiting, anorexia, or abdominal pain, and 20% to 30% may become jaundiced. The average time from exposure to symptoms is six to seven weeks (MMWR 1998). Most people infected with HCV (75% to 80%) go on to develop chronic hepatitis C. Individuals with chronic hepatitis C are the source for all new infections and are at increased risk for chronic liver disease, cirrhosis, and liver cancer (Bonkovsky and Mehta 2001). Chronic hepatitis is associated with chronic liver injury and inflammation. Liver injury appears to be a result of the patient's immune reaction to the virus, rather than damage by the virus itself. Chronic infection usually results in progressive fibrosis of the liver, which may progress to cirrhosis and other disease states. In the United States, HCV is the leading cause of liver disease and may account for 8,000 to 10,000 deaths per year. As of 1996, most HCV-infected individuals were between 30 and 49 years of age; thus, the number of deaths could substantially increase during the next 20 to 30 years, as this group reaches the age at which complications from liver disease usually occur (MMWR 1998, Alter *et al.* 1999).

HCV infection can be prevented by screening of the blood supply and reduction of contact with potentially contaminated fluids in health-care settings. The Occupational Safety and Health Administration has established a bloodborne pathogens standard, based on the concept of universal precautions, which requires that body fluids and materials be treated as infectious (OSHA 1992). Currently, HCV is treated with interferon-based therapies, and no vaccine is available.

Detection

HCV infection usually is confirmed by detection of antibodies against HCV proteins or by detection of HCV RNA. Anti-HCV antibodies are detected by serological assays, which have become more sensitive and specific. HCV RNA usually is detected by tests based on the polymerase chain reaction.

Exposure

The major route of HCV transmission is through contaminated blood. The major risk factor for infection is illegal intravenous drug use, which accounts for 60% of acute HCV infections in adults. Since the screening of blood and blood products for HCV began in the 1990s, blood transfusion has accounted for only a small percentage of adult HCV cases (about 3%). Other routes of transmission include sexual, perinatal, familial (at low rates), and through health-care practices, including transmission by contaminated equipment or supplies, from patient to patient (at low rates), and through occupational exposure (at low rates). In U.S. surveillance studies from 1983 to 1996, no epidemiological risk factors were identified for at least 10% of the cases of acute hepatitis C (Alter *et al.* 1999, Major *et al.* 2001).

The worldwide prevalence of HCV seropositivity based on published studies that used both enzyme immunoassays and supplemental testing is about 3% (170 million individuals). Prevalence varies geographically, ranging from 0.01% to 0.1% in the United Kingdom and Scandinavia to 17% to 26% in Egypt. Prevalence rates are unknown for much of Africa and parts of South America (Wasley and Alter 2000).

In the United States, the third National Health and Nutrition Examination Survey (NHANES III, conducted from 1988 to 1994) found that about 3 million to 4 million people were infected with HCV, based on anti-HCV assays (Alter *et al.* 1999). However, the annual incidence of HCV infection declined from 180,000 in the mid 1980s to 28,000 by 1995, probably as a result of testing of blood donors and decreased numbers of cases among intravenous drug users (Alter 1997). Based on NHANES data for 1999 through 2002, about 4.1 million people (95% confidence interval = 3.4 million to 4.9 million) were anti-HCV-positive, with peak prevalence (4.3%) among individuals aged 40 to 49 years. A large percentage (85.1%) of anti-HCV-positive individuals aged 20 to 59 years had a risk factor such as abnormal serum ALT levels, a history of injection drug use, or a history of blood transfusion before 1992 (Armstrong *et al.* 2006).

Regulations

Food and Drug Administration (FDA)

Regulations have been established to guard against the spread of hepatitis C through donation of blood, serum, and human immune globulin, including requirements for donor screening, product testing, and product labeling.

Regulations in 21 CFR 1270 and 1271 prescribe procedures, including donor screening and tissue testing, to ensure that tissues intended for human transplant or other human cells, tissues, and cellular and tissue-based products are free of hepatitis C.

Each donation of blood or blood product to be used in preparing a biological product shall be tested for the presence of hepatitis C surface antigen.

Occupational Safety and Health Administration (OSHA)

All work-related needlestick injuries and cuts from sharp objects that are contaminated with another person's blood or other potentially infectious material must be recorded.

First-aid training program trainees must have adequate instruction in the value of universal precautions for preventing infectious diseases.

Comprehensive regulations have been developed for employers to develop, and adhere to, exposure-control plans for bloodborne pathogens.

Public Health Service (PHS)

Regulations have been established to control the spread of hepatitis from hemodialysis treatment.

References

- Alter MJ. 1997. Epidemiology of hepatitis C. *Hepatology* 26(3 Suppl 1): 62S-65S.
- Alter MJ, Kruszon-Moran D, Nainan OV, McQuillan GM, Gao F, Moyer LA, Kaslow RA, Margolis HS. 1999. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *N Engl J Med* 341(8): 556-562.
- Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MH. 2006. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Int Med* 144 (10): 705-714.
- Bonkovsky HL, Mehta S. 2001. Hepatitis C: a review and update. *J Am Acad Dermatol* 44(2): 159-182.
- Bralet MP, Regimbeau JM, Pineau P, Dubois S, Loas G, Degos F, et al. 2000. Hepatocellular carcinoma occurring in nonfibrotic liver: epidemiologic and histopathologic analysis of 80 French cases. *Hepatology* 32(2): 200-204.
- Bukh JR, Miller H, Purcell RH. 1995. Genetic heterogeneity of hepatitis C virus: quasispecies and genotypes. *Semin Liver Dis* 15(1): 41-63.
- Craig JR, Klatt EC, Yu M. 1991. Role of cirrhosis and the development of HCC: evidence from histologic studies and large population studies. In *Etiology, Pathology, and Treatment of Hepatocellular Carcinoma in North America*. Tabor E, Di Bisceglie AM, Purcell RH, eds. The Woodlands, TX: Portfolio Publishing. pp. 177-190.
- Donato F, Boffetta P, Puoti M. 1998. A meta-analysis of epidemiological studies on the combined effect of hepatitis B and C virus infections in causing hepatocellular carcinoma. *Int J Cancer* 75(3): 347-354.
- Fong TL, Shindo M, Feinstone SM, Hoofnagle JH, Di Bisceglie AM. 1991. Detection of replicative intermediates of hepatitis C viral RNA in liver and serum of patients with chronic hepatitis C. *J Clin Invest* 88(3): 1058-1060.
- He LF, Alling D, Popkin T, Shapiro M, Alter HJ, Purcell RH. 1987. Determining the size of non-A, non-B hepatitis virus by filtration. *J Infect Dis* 156(4): 636-640.
- Huang H, Fujii H, Sankila A, Mahler-Araujo BM, Matsuda M, Cathomas G, Ohgaki H. 1999. Beta-catenin mutations are frequent in human hepatocellular carcinomas associated with hepatitis C virus infection. *Am J Pathol* 155(6): 1795-1801.
- IARC. 1994. Hepatitis C virus. In *Hepatitis viruses*. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 59. Lyon, France: International Agency for Research on Cancer. pp. 165-221.
- Koike K, Moriya K, Kimura S. 2002. Role of hepatitis C virus in the development of hepatocellular carcinoma: transgenic approach to viral hepatocarcinogenesis. *J Gastroenterol Hepatol* 17(4): 394-400.
- Laurent-Puig P, Legoix P, Bluteau O, Belghiti J, Franco D, Binot F, et al. 2001. Genetic alterations associated with hepatocellular carcinomas define distinct pathways of hepatocarcinogenesis. *Gastroenterology* 120(7): 1763-1773.
- Lerat H, Honda M, Beard MR, Loesch K, Sun J, Yang Y, et al. 2002. Steatosis and liver cancer in transgenic mice expressing the structural and nonstructural proteins of hepatitis C virus. *Gastroenterology* 122(2): 352-365.
- Linke HK, Miller MF, Peterson DA, Muchmore E, Lesniewski RR, Carrick RJ, Gagne GD, Popper H. 1987. Documentation of non-A, non-B hepatitis in a chimpanzee with hepatocellular carcinoma. In *Hepadna Viruses*. Robinson W, Koike K, Well H, eds. New York: Alan R. Liss. pp. 357-370.
- Major M, Rehmann B, Feinstone SM. 2001. Hepatitis C viruses. In *Field's Virology*. Knipe DM, Howley PM, eds. Philadelphia: Lippincott Williams & Wilkins. pp. 1127-1161.
- MMWR. 1998. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. *Morbidity Mortal Wkly Rep* 47(RR19): 1-39.
- Moriya K, Fujie H, Shintani Y, Yotsuyanagi H, Tsutsumi T, Ishibashi K, et al. 1998. The core protein of hepatitis C virus induces hepatocellular carcinoma in transgenic mice. *Nat Med* 4(9): 1065-1067.
- Muchmore E, Popper H, Peterson DA, Miller MF, Lieberman HM. 1988. Non-A, non-B hepatitis-related hepatocellular carcinoma in a chimpanzee. *J Med Primatol* 17(5): 235-246.
- NTP. 2003. *Report on Carcinogens Background Document for Hepatitis C*. National Toxicology Program. http://ntp.niehs.nih.gov/ntp/newhomero/roc11/HCV_RG2Public.pdf.
- OSHA. 1992. *Bloodborne Pathogens Final Standard: Summary of Key Provisions*. Fact Sheet No. OSHA 92-46. Occupational Safety and Health Administration. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=FACT_SHEETS&p_id=139.
- Ray RB, Lagging LM, Meyer K, Ray R. 1996. Hepatitis C virus core protein cooperates with ras and transforms primary rat embryo fibroblasts to tumorigenic phenotype. *J Virol* 70(7): 4438-4443.
- Robertson B, Myers G, Howard C, Brettin T, Bukh J, Gaschen B, et al. 1998. Classification, nomenclature, and database development for hepatitis C virus (HCV) and related viruses: proposals for standardization. International Committee on Virus Taxonomy. *Arch Virol* 143(12): 2493-2503.
- Rosenberg S. 2001. Recent advances in the molecular biology of hepatitis C virus. *J Mol Biol* 313(3): 451-464.
- Simmonds P, Holmes EC, Cha TA, Chan SW, McOmish F, Irvine B, et al. 1993. Classification of hepatitis C virus into six major genotypes and a series of subtypes by phylogenetic analysis of the NS-5 region. *J Gen Virol* 74(Pt 11): 2391-2399.
- Simmonds P. 1995. Variability of hepatitis C virus. *Hepatology* 21(2): 570-583.
- Takayama T, Makuuchi M, Hirohashi S, Sakamoto M, Okazaki N, Takayasu K, et al. 1990. Malignant transformation of adenomatous hyperplasia to hepatocellular carcinoma. *Lancet* 336(8724): 1150-1153.
- Ueta T, Ikeguchi M, Hirooka Y, Kaibara N, Terada T. 2002. Beta-catenin and cyclin D1 expression in human hepatocellular carcinoma. *Oncol Rep* 9(6): 1197-1203.
- Wasley A, Alter MJ. 2000. Epidemiology of hepatitis C: geographic differences and temporal trends. *Semin Liver Dis* 20(1): 1-16.
- Xie ZC, Riezu-Boj JJ, Lasarte JJ, Guillen J, Su JH, Civeira MP, Prieto J. 1998. Transmission of hepatitis C virus infection to tree shrews. *Virology* 244(2): 513-520.

Heterocyclic Amines (Selected)

Also known as HCAs

Introduction

Heterocyclic amines (HCAs) are formed during the cooking of meat, by condensation of creatinine with amino acids. Four individual HCAs are listed in the Report on Carcinogens as *reasonably anticipated to be a human carcinogen* (in separate listings):

- 2-Amino-3,4-dimethylimidazo[4,5-f]quinoline (MeIQ) was first listed in the *Eleventh Report on Carcinogens* (2004).
- 2-Amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx) was first listed in the *Eleventh Report on Carcinogens* (2004).
- 2-Amino-3-methylimidazo[4,5-f]quinoline (IQ) was first listed in the *Tenth Report on Carcinogens* (2002).
- 2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) was first listed in the *Eleventh Report on Carcinogens* (2004).

The profiles for these four HCAs follow. The evidence for carcinogenicity from cancer studies in experimental animals and humans is discussed separately for each HCA. However, most of the information on mechanisms of carcinogenesis, properties, use, production, exposure, and regulations is common to all four listed HCAs and therefore is combined into one section following the discussions of cancer studies.

Note on Cancer Studies of Selected HCAs in Humans

Epidemiological evidence suggests that consumption of well-done or grilled meat may be associated with increased cancer risk in humans. However, the presence of an individual HCA in cooked meat is highly correlated with the presence of other HCAs and with many other constituents, including protein, animal fat, nitrosamines, and substances other than HCAs formed during cooking, such as polycyclic aromatic hydrocarbons. Furthermore, the carcinogenic effects of these HCAs may be inhibited or enhanced by many factors, including interactions of HCA mixtures. It is therefore difficult for human epidemiological studies to establish associations between cancer risk and specific HCAs. For each of these four selected HCAs, the data from epidemiological studies are insufficient to evaluate whether the increased cancer risk is due specifically to consumption of that particular HCA in food (NTP 2002).

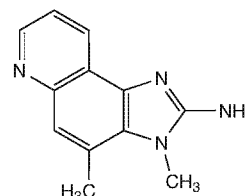
2-Amino-3,4-dimethylimidazo[4,5-f]quinoline

CAS No. 77094-11-2

Reasonably anticipated to be a human carcinogen

First listed in the *Eleventh Report on Carcinogens* (2004)

Also known as MeIQ



Carcinogenicity

MeIQ is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals and supporting genotoxicity data.

Cancer Studies in Experimental Animals

Oral exposure to MeIQ caused tumors at several different tissue sites in mice and rats. In mice of both sexes, MeIQ increased the combined incidence of benign and malignant forestomach tumors (papilloma, squamous-cell carcinoma, and sarcoma). In female mice, it also caused cancer of the cecum and colon (adenocarcinoma) and increased the combined incidence of benign and malignant liver tumors (fibrosarcoma and hepatocellular adenoma and carcinoma). In rats of both sexes, MeIQ increased the combined incidence of benign and malignant colon tumors (adenoma and adenocarcinoma) and caused cancer of the oral cavity and Zymbal gland (squamous-cell carcinoma). In addition, MeIQ caused skin cancer (squamous-cell carcinoma) in male rats and cancer of the mammary gland (adenocarcinoma) in female rats (NTP 2002).

Cancer Studies in Humans

The evidence from epidemiological studies is inadequate to evaluate the relationship between human cancer and exposure specifically to MeIQ. In one case-control study, MeIQ intake was associated with increased risks for rectal and colon cancer but not for urinary-bladder or kidney cancer (Augustsson *et al.* 1999).

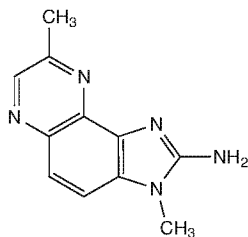
2-Amino-3,8-dimethylimidazo[4,5-f]quinoxaline

CAS No. 77500-04-0

Reasonably anticipated to be a human carcinogen

First listed in the *Eleventh Report on Carcinogens* (2004)

Also known as MeIQx



Carcinogenicity

MeIQx is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals and supporting genotoxicity data.

Cancer Studies in Experimental Animals

MeIQx caused tumors in two rodent species, at several different tissue sites, and by two different routes of exposure. Oral exposure to MeIQx increased the combined incidence of benign and malignant liver tumors (hepatocellular adenoma and carcinoma) in mice and rats of both sexes and the combined incidence of benign and malignant lung tumors (adenoma and adenocarcinoma) in female mice. It also caused lymphoma and leukemia in male mice. In rats, orally administered MeIQx also increased the combined incidence of benign and malignant Zymbal-gland tumors (sebaceous-gland adenoma and squamous-cell papilloma and carcinoma) in both sexes, and it caused skin cancer in males and cancer of the clitoral gland in fe-

males (squamous-cell carcinoma in both cases). Newborn mice exposed to MeIQx by intraperitoneal injection developed benign liver tumors (hepatocellular adenoma). In cynomolgus monkeys, MeIQx administered by stomach tube for 84 months did not cause cancer. This finding was attributed to a low level of metabolic activation of MeIQx via N-hydroxylation in this species; however, the study period may not have been long enough for detection of tumors (NTP 2002).

In rats, administration of N-hydroxy-MeIQx (a metabolite of MeIQx) by intraperitoneal injection caused soft-tissue tumors at the injection site (NTP 2002).

Cancer Studies in Humans

The evidence from epidemiological studies is inadequate to evaluate the relationship between human cancer and exposure specifically to MeIQx. Case-control studies (one study for each tissue site) suggested that MeIQx may increase the risk of benign colon tumors (adenoma) (Sinha *et al.* 2001) and lung cancer (Sinha *et al.* 2000b). MeIQx intake was not associated with cancer risk in case-control studies of urinary-bladder, kidney, or colon cancer (Augustsson *et al.* 1999). The results for breast cancer were conflicting, with two studies reporting increased risk (De Stefani *et al.* 1997, Sinha *et al.* 2000a) and one study reporting decreased risk (Delfino *et al.* 2000).

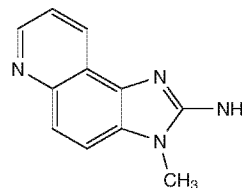
2-Amino-3-methylimidazo[4,5-f]quinoline

CAS No. 76180-96-6

Reasonably anticipated to be a human carcinogen

First listed in the *Tenth Report on Carcinogens* (2002)

Also known as IQ



Carcinogenicity

IQ is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

IQ caused tumors in several species of experimental animals, at several different tissue sites, and by several different routes of exposure. In rats of both sexes, oral exposure to IQ caused cancer of the liver (hepatocellular carcinoma), large intestine (adenocarcinoma), and Zymbal gland (squamous-cell carcinoma). It also caused cancer of the mammary gland (adenocarcinoma) and clitoral gland (squamous-cell carcinoma) in female rats and cancer of the small intestine (adenocarcinoma) and skin (squamous-cell carcinoma) in male rats. In mice of both sexes, oral exposure to IQ increased the combined incidences of benign and malignant tumors of the liver (hepatocellular adenoma and carcinoma), forestomach (papilloma and squamous-cell carcinoma), and lung (adenoma and adenocarcinoma). Newborn mice administered IQ by intraperitoneal injection developed benign and malignant liver tumors (hepatocellular adenoma and carcinoma). Male rats administered IQ by intrarectal infusion developed cancer of the colon (carcinoma) and skin (squamous-cell carcinoma) and benign liver tumors (hepatocellular adenoma). In cynomolgus mon-

keys, IQ administered orally caused liver cancer (hepatocellular carcinoma) (NTP 1999).

Cancer Studies in Humans

The evidence from epidemiological studies is inadequate to evaluate the relationship between human cancer and exposure specifically to IQ. One case-control study suggested that IQ intake increased the risk of breast cancer (De Stefani *et al.* 1997), but another case-control study found no association between IQ and cancer of the colon, rectum, urinary bladder, or kidney (Augustsson *et al.* 1999).

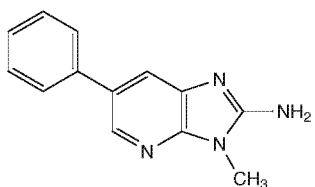
2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine

CAS No. 105650-23-5

Reasonably anticipated to be a human carcinogen

First listed in the *Eleventh Report on Carcinogens* (2004)

Also known as PhIP



Carcinogenicity

PhIP is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals and supporting genotoxicity data.

Cancer Studies in Experimental Animals

PhIP caused tumors in two rodent species, at several different tissue sites, and by two different routes of exposure. Oral exposure to PhIP caused lymphoma in mice of both sexes and in male rats. In rats, it also caused prostate cancer (carcinoma) and cancer of the small intestine and colon (adenocarcinoma) and in males and mammary-gland cancer (adenocarcinoma) in females. In a short-term study using mice with a mutation that made them susceptible to intestinal and mammary-gland tumors, oral administration of PhIP increased the combined incidence of benign and malignant tumors of the small intestine (adenoma and adenocarcinoma) in males. PhIP administered to newborn male mice by intraperitoneal injection caused benign liver tumors (hepatocellular adenoma) (NTP 2002).

N-hydroxy-PhIP (a metabolite of PhIP) administered by intraperitoneal injection caused intestinal polyps in *Apc* knockout mice (which are unable to produce the tumor-suppressor protein APC). In ACI/Seg rats (a strain with high spontaneous incidence of prostate cancer) administered *N*-hydroxy-PhIP by intraperitoneal injection, the incidences of colon tumors and rare urinary-bladder tumors were increased, though not significantly (NTP 2002).

Cancer Studies in Humans

The evidence from epidemiological studies is inadequate to evaluate the relationship between human cancer and exposure specifically to PhIP. Case-control studies suggest that PhIP may increase the risk of breast or stomach cancer. However, the association with stomach cancer was based on only one study (De Stefani *et al.* 1998), and the association with breast cancer was found in two of three studies (De Stefani *et al.* 1997, Delfino *et al.* 2000, Sinha *et al.* 2000a). No association between PhIP intake and cancer risk was found in case-

control studies of urinary-bladder, kidney, lung, colon, or prostate cancer (Augustsson *et al.* 1999, Norrish *et al.* 1999, Sinha *et al.* 2000b). PhIP intake was associated with increased risk of benign colon tumors (adenoma) in one study, but the risk was not significantly increased when the statistical analysis controlled for intake of other HCAs (Sinha *et al.* 2001).

Heterocyclic Amines (Selected)

Studies on Mechanisms of Carcinogenesis

Studies have consistently shown that MeIQ, MeIQx, IQ, and PhIP cause mutations in most test systems, including bacteria, rodents exposed *in vivo*, and cultured rodent and human cells. Moreover, compared with other well-known mutagens, such as benzo[a]pyrene, these HCAs show a high degree of potency. MeIQ, MeIQx, IQ, and PhIP also caused sister chromatid exchange, micronucleus formation, and unscheduled DNA synthesis, and most of these HCAs induced DNA damage and chromosomal aberrations in *in vivo* studies in rodents and in *in vitro* studies with human and rodent cell cultures (IARC 1993, NTP 2002).

When ingested by humans or administered orally to experimental animals, HCAs are readily absorbed and rapidly distributed. They are metabolized by both phase I (activation) and phase II (conjugation) enzymes. The major phase I activation pathway is *N*-hydroxylation by the enzyme CYP1A2 (a member of the cytochrome P450 family). Further activation by phase II enzymes, in the liver or in other tissues, is necessary for formation of the aryl nitrenium ion, which ultimately binds to DNA (NTP 2002).

HCA-induced DNA adducts have been characterized and detected in humans and other mammalian species both *in vitro* and *in vivo*, and the major adduct for each HCA is similar in all species examined. In humans, DNA adducts form at dietarily relevant levels of HCA exposure and usually are present at higher frequencies than in rodents administered an equivalent dose. HCA-induced adducts have been identified in human colon tissue, breast tissue, and prostate tumors. The DNA adduct data indicate that metabolic activation of HCAs is more efficient in humans than in experimental animals and that rapid acetylators (individuals who produce an efficient version of the enzyme *N*-acetyltransferase) may be at higher risk of cancer than slow acetylators (individuals who produce less-efficient versions of this enzyme). In studies with experimental animals, HCA-induced DNA adducts were formed in a dose-dependent manner and were associated with carcinogenesis (NTP 2002).

Mutations involving guanine (such as G:C to T:A transversions) have been detected in proto-oncogenes and tumor-suppressor genes, including *Ki-ras*, *Ha-ras*, *Apc*, *p53*, and β -*catenin*, suggesting that HCA-induced adducts are involved. The observed mutation patterns provide evidence for a mutational profile or "fingerprint" for PhIP-induced colon tumors and MeIQ-induced forestomach and Zymbal-gland tumors in mice (NTP 2002).

Properties

MeIQ, MeIQx, IQ, and PhIP are heterocyclic amines formed by condensation of creatinine with amino acids during the cooking of meat. (Creatinine is a breakdown product of creatine, an important constituent of muscle.) All of these HCAs share a common imidazole ring structure with an exocyclic amino group and, therefore, are known chemically as amino-imidazoazaarenes. Most HCAs, including MeIQ, MeIQx, and IQ, are fully planar aromatic structures with no bulky out-of-plane functionalities; however, PhIP possesses a phenyl moiety that is not necessarily coplanar with the main bicyclic imidazopyridine. All of these HCAs occur as crystalline solids and are soluble in

dimethylsulfoxide or methanol. Physical and chemical properties of MeIQ, MeIQx, IQ, and PhIP are listed in the following table.

Property	MeIQ	MeIQx	IQ	PhIP
Molecular weight	212.2	213.2	198.2	224.1
Color	pale orange to brown	yellow-green	light tan	gray-white
Melting point (°C)	296 to 298	295 to 300	> 300	327 to 328
Log K_{ow}	1.822			
Extinction coefficient	48,000 at 265 nm	41,000 at 273 nm	51,500 at 264 nm	19,400 at 316 nm

Sources: IARC 1993, Knize *et al.* 1995.

Use

MeIQ, MeIQx, IQ, and PhIP have no known commercial uses (IARC 1993).

Production

MeIQ, MeIQx, IQ, and PhIP are produced in small quantities for research purposes (IARC 1993). They are formed naturally during the cooking of muscle-derived foods (meat and fish) as by-products of the Maillard (or browning) reaction (Robbana-Barnat *et al.* 1996, Felton *et al.* 2000). It is postulated that the amino-imidazo part of HCAs is formed from creatine, while the remaining parts of the compound are likely formed from Strecker degradation products, such as pyridines or pyrazines, which are formed in the Maillard reaction between hexose sugars and amino acids (Jägerstad *et al.* 1984, Skog *et al.* 1998). Formation of HCAs in food reportedly is affected by temperature, processing time, acidity, precursor concentrations, and types of amino acid present (Keating *et al.* 1999). In general, higher temperatures and longer cooking times increase the amount of HCAs produced (Knize *et al.* 1994, Skog *et al.* 1995). HCA formation also increases with cooking methods that use direct or efficient transfer of heat from the source to the food; frying or grilling of muscle meats produces more HCAs than do indirect-heat methods such as stewing, steaming, or poaching (Layton *et al.* 1995).

Exposure

Exposure to MeIQ, MeIQx, IQ, or PhIP occurs primarily through the consumption of cooked meats; however, HCAs have also been detected in processed food flavorings, beer, wine, and cigarette smoke. Dietary exposure to total HCAs has been estimated to range from less than 1 to 17 ng/kg of body weight per day (Layton *et al.* 1995).

Total HCA concentrations in cooked meat generally range from less than 1 to about 500 ng/g (0.001 to 0.5 ppm) but usually are less than 100 ng/g (Layton *et al.* 1995, Sinha *et al.* 1995, 1998a, 1998b, Knize *et al.* 1998, Salmon *et al.* 2000). Pan residues usually contain higher HCA concentrations than the meat itself; therefore, gravy made from meat drippings and grease may have relatively high concentrations of HCAs. In four studies (reviewed by Keating *et al.* 1999), total daily HCA intakes (including MeIQx, IQ, and PhIP, but not MeIQ) ranged from 160 to 1,800 ng per person. In general, the dietary intake of these four HCAs is greatest for PhIP, followed by MeIQx, IQ, and MeIQ.

As discussed above (under Production), the concentration of HCAs in food is a function of cooking method; dietary intake is therefore a function of cooking method, doneness preference, and consumption frequency (Keating *et al.* 1999). Several studies have reported on possible methods for reducing dietary HCA (Skog *et al.* 1997, Knize *et al.* 1999, Salmon *et al.* 2000). Effective methods include using cooking temperatures below 200°C (392°F), turning meat more frequently during cooking, precooking meat in a microwave oven for at least two minutes and draining off the liquid before conventional

cooking, and applying marinades before grilling. However, some marinades are more effective than others; PhIP and MeIQx concentrations were reduced by teriyaki sauce or turmeric-garlic sauce, but increased by a honey barbecue sauce (Nerurkar *et al.* 1999).

Occupational exposure to HCAs may occur by inhalation of aerosolized particles formed during the cooking process. PhIP and MeIQx were detected in smoke condensate formed during frying of beef patties and bacon (Thiébaud *et al.* 1995), and MeIQx was detected in aerosol from cooking of stir-fried fish (Yang *et al.* 1998). PhIP was detected in airborne particles, diesel-exhaust particles, and incineration ash from garbage-burning plants (Manabe *et al.* 1993).

Specific exposure information for each of these four HCAs follows.

MeIQ

MeIQ is found less frequently in food and generally at lower concentrations than are other HCAs, including MeIQx, PhIP, and IQ. The highest concentrations were detected in cooked fish, ranging from 0.03 to 72 ng/g; the concentrations were highest in grilled sun-dried sardines and lower in fried or broiled fish (IARC 1993, Lynch *et al.* 1995). MeIQ was found at low levels or was not detectable in cooked beef, pork, or chicken; various studies reported concentrations ranging from 0.02 ng/g (in pork) to 1.7 ng/g (in well-done bacon) (Johansson and Jägerstad 1994, Lynch *et al.* 1995). It was also detected in gravy, coffee beans, and cigarette smoke. In a Swiss population, daily MeIQ intake was estimated to be 0.6 ng/kg of body mass (Zimmerli *et al.* 2001).

MeIQx

MeIQx has been detected in beef, pork, chicken, and fish. The highest concentrations were found in well-done grilled chicken, beef (hamburger or steak), and bacon. Very-well-done grilled or barbecued chicken contained 9 ng/g, and very-well-done oven-broiled or pan-fried skinless, boneless chicken breasts contained 3 ng/g (Sinha *et al.* 1995). In one study, MeIQx concentrations in beef ranged from nondetectable to 8.2 ng/g in steak and from nondetectable to 4.6 ng/g in hamburger patties, depending on the cooking method and degree of doneness (Sinha *et al.* 1998b). Another study found that fish contained about 1.2 ng/g (Johansson and Jägerstad 1994). Pork, other than bacon, contains very little MeIQx; MeIQx was detected at 0.9 to 18 ng/g in bacon and 1.4 to 27 ng/g in bacon fat (Gross *et al.* 1993). MeIQx also occurs in processed food flavors (bouillon and gravy concentrates) and wine. In three large U.S. cohort studies (two Nurses' Health Studies and the Health Professionals Follow-Up Study), estimated mean daily intake of MeIQx ranged from 33 to 44.8 ng/g of food consumed (Byrne *et al.* 1998). Daily MeIQx intake was estimated to be 2.61 ng/kg of body mass (Layton *et al.* 1995). MeIQx also has been found in air and surface water.

IQ

IQ was originally isolated from broiled fish, fried ground beef, and beef extracts. It has since been detected in fried chicken, fried eggs, fried fish, broiled ground beef, minute steaks, meatballs, pork chops, and cigarette smoke condensate. Reported concentrations in foods range from less than 0.1 to more than 150 ng/g, with most less than 1 ng/g (IARC 1993, Skog *et al.* 1995, Chiu *et al.* 1998). However, Sinha *et al.* (1998b) did not detect IQ in hamburgers, steaks, or roast beef cooked by varying methods to three levels of doneness. The highest reported IQ concentration occurred in broiled sun-dried sardines. Daily IQ intake from meat and fish was estimated to be 0.28 ng/kg of body mass (Layton *et al.* 1995).

PhIP

PhIP is the most abundant HCA detected in foods and has been found in beef, pork, chicken, lamb, and fish. The highest concentrations were detected in very-well-done grilled chicken; however, concentrations varied considerably from study to study. High concentrations (over 100 ng/g) were found in well-done steak and hamburgers. Concentrations of PhIP in fish varied greatly according to the type of fish and method of cooking; one study reported levels ranging from 1.7 to 73 ng/g in salmon cooked at 200°C by various methods (pan broiled, oven cooked, or barbecued) for various lengths of time (Gross and Grüter 1992), but another study (Skog *et al.* 1997) reported substantially lower levels (0.02 to 2.2 ng/g) for cod and Baltic herring fillets pan fried at temperatures ranging from 150°C to 225°C. PhIP was found at lower concentrations in pork (0.1 to 2.3 ng/g). It was also detected in processed food flavors, beer, and wine at concentrations ranging from 0.01 to 480 ng/g and in cigarette smoke. In the same three large U.S. cohort studies cited above for MeIQx, mean daily PhIP intake ranged from 285.5 to 457 ng/day (Byrne *et al.* 1998). Daily PhIP intake was estimated to be 17 ng/kg of body mass (Layton *et al.* 1995). PhIP has also been found in air and surface water.

Regulations

No regulations or guidelines relevant to reduction of exposure to heterocyclic amines were identified.

References

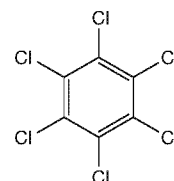
- Augustsson K, Skog K, Jagerstad M, Dickman PW, Steineck G. 1999. Dietary heterocyclic amines and cancer of the colon, rectum, bladder, and kidney: a population-based study. *Lancet* 353(9154): 703-707.
- Byrne C, Sinha R, Platz EA, Giovannucci E, Colditz GA, Hunter DJ, Speizer FE, Willett WC. 1998. Predictors of dietary heterocyclic amine intake in three prospective cohorts. *Cancer Epidemiol Biomarkers Prev* 7(6): 523-529.
- Chiu CP, Yang DY, Chen BH. 1998. Formation of heterocyclic amines in cooked chicken legs. *J Food Prot* 61(6): 712-719.
- De Stefani E, Ronco A, Mendilaharsu M, Guidobono M, Deneo-Pellegrini H. 1997. Meat intake, heterocyclic amines, and risk of breast cancer: a case-control study in Uruguay. *Cancer Epidemiol Biomarkers Prev* 6(8): 573-581.
- De Stefani E, Boffetta P, Mendilaharsu M, Carzoglio J, Deneo-Pellegrini H. 1998. Dietary nitrosamines, heterocyclic amines, and risk of gastric cancer: a case-control study in Uruguay. *Nutr Cancer* 30(2): 158-162.
- Delfino RJ, Sinha R, Smith C, West J, White E, Lin HJ, *et al.* 2000. Breast cancer, heterocyclic aromatic amines from meat and *N*-acetyltransferase 2 genotype. *Carcinogenesis* 21(4): 607-615.
- Felton JS, Jagerstad M, Knize MG, Skog K, Wakabayashi K. 2000. Contents in foods, beverages and tobacco. In *Food Borne Carcinogens Heterocyclic Amines*. Nagao M, Sugimura T, eds. West Sussex, England: John Wiley & Sons. pp. 31-71.
- Gross GA, Grüter A. 1992. Quantitation of mutagenic/carcinogenic heterocyclic aromatic amines in food products. *J Chromatogr* 592(1-2): 271-278.
- Gross GA, Turesky RJ, Fay LB, Stillwell WG, Skipper PL, Tannenbaum SR. 1993. Heterocyclic aromatic amine formation in grilled bacon, beef and fish and in grill scrapings. *Carcinogenesis* 14(11): 2313-2318.
- IARC. 1993. Heterocyclic aromatic amines. In *Some Naturally Occurring Substances: Food Items and Constituents, Heterocyclic Aromatic Amines, and Mycotoxins*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 56. Lyon, France: International Agency for Research on Cancer. pp. 165-242.
- Jagerstad M, Olsson K, Grivas S, Negishi K, Wakabayashi K, Tsuda M, Sato S, Sugimura T. 1984. Formation of 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline in a model system by heating creatinine, glycine and glucose. *Mutat Res* 126(3): 239-244.
- Johansson MA, Jagerstad M. 1994. Occurrence of mutagenic/carcinogenic heterocyclic amines in meat and fish products, including pan residues, prepared under domestic conditions. *Carcinogenesis* 15(8): 1511-1518.
- Keating GA, Layton DW, Felton JS. 1999. Factors determining dietary intakes of heterocyclic amines in cooked foods. *Mutat Res* 443(1-2): 149-156.
- Knize MG, Dolbear FA, Carroll KL, Moore DH 2nd, Felton JS. 1994. Effect of cooking time and temperature on the heterocyclic amine content of fried beef patties. *Food Chem Toxicol* 32(7): 595-603.
- Knize MG, Sinha R, Rothman N, Brown ED, Salmon CP, Levander OA, Cunningham PL, Felton JS. 1995. Heterocyclic amine content in fast-food meat products. *Food Chem Toxicol* 33(7): 545-551.
- Knize MG, Sinha R, Brown ED, Salmon CP, Levander OA, Felton JS, Rothman N. 1998. Heterocyclic amine content in restaurant-cooked hamburgers, steaks, ribs, and chicken. *J Agri Food Chem* 46(11): 4648-4651.
- Knize MG, Salmon CP, Pais P, Felton JS. 1999. Food heating and the formation of heterocyclic aromatic amine and polycyclic aromatic hydrocarbon mutagens/carcinogens. *Adv Exp Med Biol* 459: 179-193.
- Layton DW, Bogen KT, Knize MG, Hatch FT, Johnson VM, Felton JS. 1995. Cancer risk of heterocyclic amines in cooked foods: an analysis and implications for research. *Carcinogenesis* 16(1): 39-52.
- Lynch AM, Murray S, Gooderham NJ, Boobis AR. 1995. Exposure to and activation of dietary heterocyclic amines in humans. *Crit Rev Oncol Hematol* 21(1-3): 19-31.
- Manabe S, Suzuki H, Wada O, Ueki A. 1993. Detection of the carcinogen 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) in beer and wine. *Carcinogenesis* 14(5): 899-901.
- Nerurkar PV, Le Marchand L, Cooney RV. 1999. Effects of marinating with Asian marinades or western barbecue sauce on PhIP and MeIQx formation in barbecued beef. *Nutr Cancer* 34(2): 147-152.
- Norrish AE, Ferguson LR, Knize MG, Felton JS, Sharpe SJ, Jackson RT. 1999. Heterocyclic amine content of cooked meat and risk of prostate cancer. *J Natl Cancer Inst* 91(23): 2038-2044.
- NTP. 1999. *Report on Carcinogens Background Document for 2-Amino-3-Methylimidazo[4,5-f]Quinoline (IQ)*. National Toxicology Program. <http://ntp.niehs.nih.gov/ntp/newhomero/roc10/IQ.pdf>.
- NTP. 2002. *Report on Carcinogens Background Document for Heterocyclic Amines: PhIP, MeIQ and MeIQx*. National Toxicology Program. <http://ntp.niehs.nih.gov/ntp/newhomero/roc11/HCA5Pub.pdf>.
- Robbana-Barnat S, Rabache M, Rialland E, Fradin J. 1996. Heterocyclic amines: Occurrence and prevention in cooked food. *Environ Health Perspect* 104(3): 280-288.
- Salmon CP, Knize MG, Panteleakos FN, Wu RW, Nelson DO, Felton JS. 2000. Minimization of heterocyclic amines and thermal inactivation of *Escherichia coli* in fried ground beef. *J Natl Cancer Inst* 92(21): 1773-1778.
- Sinha R, Rothman N, Brown ED, Salmon CP, Knize MG, Swanson CA, *et al.* 1995. High concentrations of the carcinogen 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) occur in chicken but are dependent on the cooking method. *Cancer Res* 55(20): 4516-4519.
- Sinha R, Knize MG, Salmon CP, Brown ED, Rhodes D, Felton JS, Levander OA, Rothman N. 1998a. Heterocyclic amine content of pork products cooked by different methods and to varying degrees of doneness. *Food Chem Toxicol* 36(4): 289-297.
- Sinha R, Rothman N, Salmon CP, Knize MG, Brown ED, Swanson CA, *et al.* 1998b. Heterocyclic amine content in beef cooked by different methods to varying degrees of doneness and gravy made from meat drippings. *Food Chem Toxicol* 36(4): 279-287.
- Sinha R, Gustafson DR, Kulldorff M, Wen WQ, Cerhan JR, Zheng W. 2000a. 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine, a carcinogen in high-temperature-cooked meat, and breast cancer risk. *J Natl Cancer Inst* 92(16): 1352-1354.
- Sinha R, Kulldorff M, Swanson CA, Curtin J, Brownson RC, Alavanja MC. 2000b. Dietary heterocyclic amines and the risk of lung cancer among Missouri women. *Cancer Res* 60(14): 3753-3756.
- Sinha R, Kulldorff M, Chow WH, Denobile J, Rothman N. 2001. Dietary intake of heterocyclic amines, meat-derived mutagenic activity, and risk of colorectal adenomas. *Cancer Epidemiol Biomarkers Prev* 10(5): 559-562.
- Skog K, Steineck G, Augustsson K, Jagerstad M. 1995. Effect of cooking temperature on the formation of heterocyclic amines in fried meat products and pan residues. *Carcinogenesis* 16(4): 861-867.
- Skog K, Augustsson K, Steineck G, Stenberg M, Jagerstad M. 1997. Polar and non-polar heterocyclic amines in cooked fish and meat products and their corresponding pan residues. *Food Chem Toxicol* 35(6): 555-565.
- Skog KI, Johannsson MA, Jagerstad MI. 1998. Carcinogenic heterocyclic amines in model systems and cooked foods: A review on formation, occurrence and intake. *Food Chem Toxicol* 36(9-10): 879-896.
- Thiébaud HP, Knize MG, Kuzmicky PA, Hsieh DP, Felton JS. 1995. Airborne mutagens produced by frying beef, pork and a soy-based food. *Food Chem Toxicol* 33(10): 821-828.
- Yang CC, Jenq SN, Lee H. 1998. Characterization of the carcinogen 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline in cooking aerosols under domestic conditions. *Carcinogenesis* 19(2): 359-363.
- Zimmerli B, Rhyn P, Zoller O, Schlatter J. 2001. Occurrence of heterocyclic aromatic amines in the Swiss diet: analytical method, exposure estimation and risk assessment. *Food Addit Contam* 18(6): 533-551.

Hexachlorobenzene

CAS No. 118-74-1

Reasonably anticipated to be a human carcinogen

First listed in the *Third Annual Report on Carcinogens* (1983)



Carcinogenicity

Hexachlorobenzene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to hexachlorobenzene caused tumors in several rodent species and at two different tissue sites. Dietary administration of hexachlorobenzene caused liver tumors (hepatocellular tumors) in female rats and mice and in hamsters of both sexes. In hamsters of both sexes, it also caused blood-vessel tumors in the liver (hemangio-endothelioma) and benign thyroid-gland tumors (follicular-cell adenoma) (IARC 1979, Smith and Cabral 1980).

Since hexachlorobenzene was listed in the *Third Annual Report on Carcinogens*, additional studies in rats have been identified. Dietary exposure caused benign and malignant liver tumors (bile-duct adenoma and hepatocellular carcinoma) and benign blood-vessel tumors in the liver (hemangioma) in females and benign kidney tumors (adenoma) in both sexes. Perinatal exposure to hexachlorobenzene followed by dietary exposure for up to 130 weeks caused benign liver tumors (hepatocellular adenoma) in females, benign parathyroid-gland tumors (adenoma) in males, and benign adrenal-gland tumors (pheochromocytoma) in both sexes (IARC 1987, 2001).

Cancer Studies in Humans

At the time hexachlorobenzene was listed in the *Third Annual Report on Carcinogens*, no epidemiological studies had evaluated the relationship between human cancer and exposure specifically to hexachlorobenzene. Since then, several case-control studies, mostly of breast cancer, have been published. The International Agency for Research on Cancer concluded that there was inadequate evidence in humans for the carcinogenicity of hexachlorobenzene (IARC 2001). No association between exposure to hexachlorobenzene and breast cancer risk was found in five small case-control studies or three larger studies that assessed hexachlorobenzene exposure by measuring it in biological samples obtained close to the time of breast-cancer diagnosis. In a fourth large study, which assessed exposure from banked serum samples collected prior to diagnosis, breast-cancer risk was higher among women with higher serum concentrations of hexachlorobenzene than among women with the lowest serum concentrations, based on sampling close to the time of diagnosis; however, no dose-response relationship was observed. No significant associations between serum hexachlorobenzene concentration and risk of cancer at other tissue sites were found; however, only one study was available for each tissue site.

Since the IARC (2001) review, a number of additional studies have been conducted, mainly of breast cancer and non-Hodgkin's lymphoma. Two studies reported significantly higher serum hexachlorobenzene levels in women with breast cancer than in control subjects (Charlier *et al.* 2003, 2004), but four other studies found no significant association between serum hexachlorobenzene level and breast cancer (Lopez-Carrillo *et al.* 2002, Pavuk *et al.* 2003, Iwasaki *et al.* 2008, Itoh *et al.* 2009). One study of non-Hodgkin's lymphoma found a significant dose-related risk associated with serum hexachlorobenzene (Spinelli *et al.* 2007), and two studies found a significantly increased risk among patients with high Epstein-Barr virus antibody titers (also associated with non-Hodgkin's lymphoma) (Hardell *et al.* 2001, 2009). However, no association with non-Hodgkin's lymphoma was observed in a study using banked serum samples collected up to 20 years prior to diagnosis and analyzed for hexachlorobenzene (Cantor *et al.* 2003) or in a multicenter study of lymphoma patients using blood levels of hexachlorobenzene measured close to the time of diagnosis (Cocco *et al.* 2008).

Properties

Hexachlorobenzene is a chlorinated aromatic hydrocarbon that exists as a white needle-like crystalline solid at room temperature (HSDB

2010). It is practically insoluble in water, sparingly soluble in cold alcohol and carbon tetrachloride, and soluble in benzene, chloroform, ether, and carbon disulfide. It is stable under normal temperatures and pressures (Akron 2010). It is combustible but it does not ignite readily. When hexachlorobenzene decomposes, it emits highly toxic fumes of hydrochloric acid, other chlorinated compounds, carbon monoxide, and carbon dioxide. Physical and chemical properties of hexachlorobenzene are listed in the following table.

Property	Information
Molecular weight	284.8
Density	2.044 g/cm ³ at 23°C
Melting point	231.8°C
Boiling point	325°C
Log <i>K</i> _{ow}	5.73
Water solubility	4.7 × 10 ⁻⁶ g/L at 25°C
Vapor density relative to air	9.83

Source: HSDB 2010.

Use

No commercial uses of hexachlorobenzene as an end product in the United States were identified (ATSDR 2002). Previously, it was used as a seed-treatment fungicide for onions, sorghum, wheat, and other grains (IARC 1979). All registered pesticide uses in the United States were voluntarily cancelled in 1984 (ATSDR 2002). Hexachlorobenzene was also used as a chemical intermediate in dye manufacturing, in the synthesis of other organic chemicals, and in the production of pyrotechnic compositions for the military. It was used as a raw material for synthetic rubber, as a plasticizer for polyvinyl chloride, as a porosity controller in the manufacture of electrodes, and as a wood preservative (IARC 1979, ATSDR 2002).

Production

Commercial production of hexachlorobenzene in the United States was first reported in 1933 (IARC 1979). In 1975, 3,200 lb of hexachlorobenzene was produced, but it has not been produced commercially in the United States since the late 1970s. In 1972, an estimated 2.5 million to 4.9 million pounds of hexachlorobenzene was produced in the United States as a by-product of production of other chlorinated solvents and pesticides such as tetrachloroethylene, trichloroethylene, carbon tetrachloride, vinyl chloride, atrazine, propazine, simazine, pentachlorophenol, chlorothalonil, and pentachloronitrobenzene. In addition, hexachlorobenzene may be formed during combustion of municipal waste or in waste streams from chlor-alkali and wood-preserving plants (IARC 1979, ATSDR 2002).

In 2002, nine U.S. chemical companies produced hexachlorobenzene for on-site use and processing, as a by-product, or as an impurity (ATSDR 2002). In 2009, hexachlorobenzene was available from 19 suppliers worldwide, including 14 U.S. suppliers (ChemSources 2010). U.S. imports of hexachlorobenzene totaled about 5,400 lb in 1977 and 38,000 lb in 1982 (ATSDR 2002, HSDB 2010). Imports of hexachlorobenzene and dichlorodiphenyltrichloroethane (DDT) (reported together) have generally been low since 1989. However, 2.3 million pounds was imported in 1993 and 4.9 million pounds in 2001, even though neither hexachlorobenzene nor DDT is used in the United States (USITC 2010). Imports were zero in 2007 and 11 lb in both 2006 and 2008. U.S. exports in this category have remained at about 1 million pounds or less since 1989, reaching a low of 7,000 lb in 2008. Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of hexachlorobenzene totaled 10,000 to 500,000 lb in 1998 and 2002 (EPA 2004).

Exposure

Hexachlorobenzene is highly persistent in the environment and highly resistant to degradation; therefore, the general population may be exposed at low concentrations (ATSDR 2002). When hexachlorobenzene is released to the environment, it may be taken up by plants and animals and can bioaccumulate through the food chain. Hexachlorobenzene has been detected in terrestrial, freshwater, and marine food chains in the Great Lakes and Arctic regions. Populations with the greatest potential for exposure include those who ingest fish caught from contaminated water bodies or who reside near former manufacturing or waste-disposal sites.

According to EPA's Toxics Release Inventory, environmental releases of hexachlorobenzene ranged from over 1 million pounds in 1989 and 1991 to a low of about 12,600 lb in 1997. In 2008, 49 facilities released at total of 50,636 lb of hexachlorobenzene, mostly to on-site and off-site landfills. The majority of releases came from 5 facilities, and 12 facilities reported releases of more than 100 lb (TRI 2010). When hexachlorobenzene is released to air, it tends to remain mainly in the vapor phase and can therefore be transported great distances (for example, from temperate to polar regions). When released to water, hexachlorobenzene is strongly adsorbed to particles and sediment and is not degraded or hydrolyzed (ATSDR 2002). In the Great Lakes region, hexachlorobenzene was found in drinking and surface water and, at higher levels, in soil and sediment. In 1972, it was detected in agricultural soils where it had been used as a pesticide, at lower levels in urban soils, and at higher levels in soils near uncontrolled hazardous-waste sites. It was found at high concentrations in sediments near industrial sites at Galveston Bay, Texas (ATSDR 2002).

In dietary surveys conducted by the U.S. Food and Drug Administration, the frequency at which hexachlorobenzene was detected in foods declined from 9% in the early 1980s to less than 2% in 1994 (ATSDR 2002). Consequently, the U.S. average daily intake of hexachlorobenzene through foods declined by a factor of 5 over this period. In the FDA Total Diet Study, hexachlorobenzene was detected in 229 of 1,748 samples (13%) of 42 different foods; the highest concentration was found in butter (FDA 2006).

Hexachlorobenzene has been detected in the blood of numerous groups of people, especially indigenous populations of Arctic regions, in the blood and breast milk of pregnant and lactating women, and in the placenta and cord blood. Organochlorine compounds were found in maternal blood in circumpolar populations in Greenland, Canada, Alaska, Norway, Sweden, Iceland, Finland, and Russia (Van Oostdam *et al.* 2004). In Arctic Canada, hexachlorobenzene was detected in all samples of maternal blood, and at higher concentrations in blood from Inuit women than from Caucasian women in the region. Cord-blood plasma concentrations showed a similar trend (Butler Walker *et al.* 2003). Breast-milk concentrations of hexachlorobenzene were elevated in populations of women who ate contaminated local fish in New York State and Finland (Greizerstein *et al.* 1999, Kostyniak *et al.* 1999, Fitzgerald *et al.* 2001, Damgaard *et al.* 2006). Hexachlorobenzene was found in all blood samples from pregnant women in an agricultural community in California (Fenster *et al.* 2006). The diet of the Inuit population in Greenland was studied to determine the source of the high and increasing concentration of hexachlorobenzene. The blood levels of hexachlorobenzene in Greenland Arctic populations appeared to correlate with consumption of meals containing seal and whale (Deutch *et al.* 2004, 2006). Hexachlorobenzene was detected in all adipose tissue samples collected at autopsy from Greenlanders (Dewailly *et al.* 1999). Hexachlorobenzene was detected in 98% of the blood samples collected from Akwesasne Mohawk youth living along the St. Lawrence River in New York State and Quebec; levels were somewhat higher in youths who had been breastfed as

infants (Schell *et al.* 2003). In a study of consumers of sport fish in New York State, the mean blood hexachlorobenzene concentration was not significantly greater than that of nonconsumers of sport fish (Bloom *et al.* 2005).

The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 1,038 workers at 10 facilities, including 26 women, potentially were exposed to hexachlorobenzene (NIOSH 1990). The largest numbers of exposed workers were chemical technicians (467 workers) and their supervisors (187 workers). Occupations with the highest potential for exposure included fungicide application, organic-chemical synthesis, synthetic-rubber production, seed disinfection, pesticide production, and wood preservation.

Regulations

Department of Transportation (DOT)

Hexachlorobenzene is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture of hexachlorobenzene is subject to certain provisions for the control of volatile organic compound emissions.

Urban Air Toxics Strategy: Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Effluent Guidelines: Chlorinated benzenes are listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.00028 µg/L; based on fish or shellfish consumption only = 0.00029 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxic characteristic leaching procedure threshold = 0.13 mg/L.

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of hexachlorobenzene = U127, F024, F025, K016, K018, K030, K042, K085, K149, K150, K151.

Listed as a hazardous constituent of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.001 mg/L.

Food and Drug Administration (FDA)

Maximum permissible level in bottled water = 0.001 mg/L.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.002 mg/m³.

References

- Akron. 2010. *The Chemical Database*. The Department of Chemistry at the University of Akron. <http://uill.chemistry.uakron.edu/erd> and search on CAS number. Last accessed: 1/8/2010.
- ATSDR. 2002. *Toxicological Profile for Hexachlorobenzene*. Agency for Toxic Substances and Disease Registry. <http://www.atsdr.cdc.gov/ToxProfiles/tp90.pdf>.
- Bloom MS, Vena JE, Swanson MK, Moysich KB, Olson JR. 2005. Profiles of *ortho*-polychlorinated biphenyl congeners, dichlorodiphenyldichloroethylene, hexachlorobenzene, and Mirex among male Lake Ontario sportfish consumers: the New York State angler cohort study. *Environ Res* 97(2): 178-194.
- Butler Walker J, Seddon L, McMullen E, Houseman J, Tofflemire K, Corriveau A, *et al.* 2003. Organochlorine levels in maternal and umbilical cord blood plasma in Arctic Canada. *Sci Total Environ* 302(1-3): 27-52.
- Cantor KP, Strickland PT, Brock JW, Bush D, Helzlsouer K, Needham LL, Zahm SH, Comstock GW, Rothman N. 2003. Risk of non-Hodgkin's lymphoma and prediagnostic serum organochlorines: β -hexachlorocyclohexane, chlordane/heptachlor-related compounds, dieldrin, and hexachlorobenzene. *Environ Health Perspect* 111(2): 179-183.
- Charlier C, Albert A, Herman P, Hamoir E, Gaspard U, Meurisse M, Plomteux G. 2003. Breast cancer and serum organochlorine residues. *Occup Environ Med* 60(5): 348-351.
- Charlier C, Foldart JM, Pitance F, Herman P, Gaspard U, Meurisse M, Plomteux G. 2004. Environmental dichlorodiphenyltrichloroethane or hexachlorobenzene exposure and breast cancer: Is there a risk? *Clin Chem Lab Med* 42(2): 222-227.

ChemSources. 2010. *Chem Sources - Chemical Search*. Chemical Sources International, Inc. <http://www.chemsources.com/chemonline.html> and search on hexachlorobenzene. Last accessed: 1/8/2010.

Cocco P, Brennan P, Ibba A, de Sanjose Llongueras S, Maynadie M, Nieters A, et al. 2008. Plasma polychlorobiphenyl and organochlorine pesticide level and risk of major lymphoma subtypes. *Occup Environ Med* 65(2): 132-140.

Damgaard IN, Skakkebaek NE, Toppari J, Virtanen HE, Shen H, Schramm KW, et al. 2006. Persistent pesticides in human breast milk and cryptorchidism. *Environ Health Perspect* 114(7): 1133-1138.

Deutch B, Pedersen HS, Hansen JC. 2004. Dietary composition in Greenland 2000, plasma fatty acids and persistent organic pollutants. *Sci Total Environ* 331(1-3): 177-188.

Deutch B, Dyerberg J, Pedersen HS, Asmund G, Moller P, Hansen JC. 2006. Dietary composition and contaminants in north Greenland, in the 1970s and 2004. *Sci Total Environ* 370(2-3): 372-381.

Dewailly E, Mulvad G, Pedersen HS, Ayotte P, Demers A, Weber JP, Hansen JC. 1999. Concentration of organochlorines in human brain, liver, and adipose tissue autopsy samples from Greenland. *Environ Health Perspect* 107(10): 823-828.

EPA. 2004. *Non-confidential IUR Production Volume Information*. U.S. Environmental Protection Agency. <http://www.epa.gov/oppt/iur/tools/data/2002-vol.html> and search on CAS number.

FDA. 2006. *Total Diet Study Market Baskets 1991-3 through 2003-4*. U.S. Food and Drug Administration. <http://www.fda.gov/downloads/Food/FoodSafety/FoodContaminantsAdulteration/TotalDietStudy/UCM184304.pdf>. <http://www.cfsan.fda.gov/~acrobat/tds1byps.pdf>

Fenster L, Eskenazi B, Anderson M, Bradman A, Harley K, Hernandez H, Hubbard A, Barr DB. 2006. Association of *in utero* organochlorine pesticide exposure and fetal growth and length of gestation in an agricultural population. *Environ Health Perspect* 114(4): 597-602.

Fitzgerald EF, Hwang SA, Deres DA, Bush B, Cook K, Worswick P. 2001. The association between local fish consumption and DDE, mirex, and HCB concentrations in the breast milk of Mohawk women at Akwesasne. *J Expo Anal Environ Epidemiol* 11(5): 381-388.

Greizerstein HB, Stinson C, Mendola P, Buck GM, Kostyniak PJ, Vena JE. 1999. Comparison of PCB congeners and pesticide levels between serum and milk from lactating women. *Environ Res* 80(3): 280-286.

Hardell E, Eriksson M, Lindstrom G, Van Bavel B, Linde A, Carlberg M, Liljegren G. 2001. Case-control study on concentrations of organohalogen compounds and titers of antibodies to Epstein-Barr virus antigens in the etiology of non-Hodgkin lymphoma. *Leuk Lymphoma* 42(4): 619-629.

Hardell K, Carlberg M, Hardell L, Bjornfoth H, Ericson Jogsten I, Eriksson M, Van Bavel B, Lindstrom G. 2009. Concentrations of organohalogen compounds and titres of antibodies to Epstein-Barr virus antigens and the risk for non-Hodgkin lymphoma. *Oncol Rep* 21(6): 1567-1576.

HSDB. 2010. *Hazardous Substances Data Bank*. National Library of Medicine. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number. Last accessed: 1/8/2010.

IARC. 1979. Hexachlorobenzene. In *Some Halogenated Hydrocarbons*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 20. Lyon, France: International Agency for Research on Cancer. pp. 155-178.

IARC. 1987. Hexachlorobenzene. In *Overall Evaluations of Carcinogenicity*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, suppl. 7. Lyon, France: International Agency for Research on Cancer. pp. 219-220.

IARC. 2001. Hexachlorobenzene. In *Some Thyrotropic Agents*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 79. Lyon, France: International Agency for Research on Cancer. pp. 493-568.

Itoh H, Iwasaki M, Hanaoka T, Kasuga Y, Yokoyama S, Onuma H, Nishimura H, Kusama R, Tsugane S. 2009. Serum organochlorines and breast cancer risk in Japanese women: a case-control study. *Cancer Causes Control* 20(5): 567-580.

Iwasaki M, Inoue M, Sasazuki S, Kurahashi N, Itoh H, Usuda M, Tsugane S. 2008. Plasma organochlorine levels and subsequent risk of breast cancer among Japanese women: a nested case-control study. *Sci Total Environ* 402(2-3): 176-183.

Kostyniak PJ, Stinson C, Greizerstein HB, Vena J, Buck G, Mendola P. 1999. Relation of Lake Ontario fish consumption, lifetime lactation, and parity to breast milk polychlorobiphenyl and pesticide concentrations. *Environ Res* 80(2 Pt 2): S166-S174.

Lopez-Carrillo L, Lopez-Cervantes M, Torres-Sanchez L, Blair A, Cebrian ME, Garcia RM. 2002. Serum levels of beta-hexachlorocyclohexane, hexachlorobenzene and polychlorinated biphenyls and breast cancer in Mexican women. *Eur J Cancer Prev* 11(2): 129-135.

NIOSH. 1990. *National Occupational Exposure Survey (1981-83)*. National Institute for Occupational Safety and Health. Last updated: 7/1/90. <http://www.cdc.gov/noes/noes1/a1753sic.html>.

Pavuk M, Cerhan JR, Lynch CF, Kocan A, Petrik J, Chovancova J. 2003. Case-control study of PCBs, other organochlorines and breast cancer in Eastern Slovakia. *J Expo Anal Environ Epidemiol* 13(4): 267-275.

Schell LM, Hubicki LA, DeCaprio AP, Gallo MV, Ravenscroft J, Tarbell A, Jacobs A, David D, Worswick P. 2003. Organochlorines, lead, and mercury in Akwesasne Mohawk youth. *Environ Health Perspect* 111(7): 954-961.

Smith AG, Cabral JR. 1980. Liver-cell tumours in rats fed hexachlorobenzene. *Cancer Lett* 11(2): 169-172.

Spinelli JJ, Ng CH, Weber JP, Connors JM, Gascoyne RD, Lai AS, et al. 2007. Organochlorines and risk of non-Hodgkin lymphoma. *Int J Cancer* 121(12): 2767-2775.

TRI. 2009. *TRI Explorer Chemical Report*. U.S. Environmental Protection Agency. Last updated: 3/19/09. <http://www.epa.gov/triexplorer> and select Hexachlorobenzene.

USITC. 2010. *USITC Interactive Tariff and Trade DataWeb*. United States International Trade Commission. http://dataweb.usitc.gov/scripts/user_set.asp and search on HTS no. 290362. Last accessed: 1/8/2010.

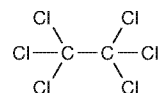
Van Oostdam JC, Dewailly E, Gilman A, Hansen JC, Odland JO, Chashchin V, et al. 2004. Circumpolar maternal blood contaminant survey, 1994-1997 organochlorine compounds. *Sci Total Environ* 330(1-3): 55-70.

Hexachloroethane

CAS No. 67-72-1

Reasonably anticipated to be a human carcinogen

First listed in the *Seventh Annual Report on Carcinogens* (1994)



Carcinogenicity

Hexachloroethane is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to hexachloroethane caused tumors in two rodent species and at several different tissue sites. Administration of hexachloroethane by stomach tube caused liver cancer (hepatocellular carcinoma) in mice of both sexes and benign and malignant kidney tumors (renal-tubular adenoma and carcinoma) in male rats (NCI 1978, IARC 1979, NTP 1989). The incidence of benign adrenal-gland tumors (pheochromocytoma) also was marginally increased in male rats.

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to hexachloroethane. Since hexachloroethane was listed in the *Seventh Annual Report on Carcinogens*, one additional epidemiological study has been identified. In a cohort study of workers at aluminum foundries and smelters in Sweden, no association was observed between cancer incidence and exposure to hexachloroethane (IARC 1999).

Properties

Hexachloroethane is a chlorinated alkane that exists at room temperature as a colorless crystalline solid with a camphor-like odor. It is practically insoluble in water, soluble in ethanol, benzene, chloroform, and oils, and very soluble in diethyl ether and tetrachloroethylene (Akron 2009, HSDB 2009). Hexachloroethane is stable under normal temperatures and pressures and is considered nonflammable; however, it is incompatible or reactive with alkalis and with metals such as zinc, cadmium, aluminum, hot iron, and mercury (NIOSH 2005). Physical and chemical properties of hexachloroethane are listed in the following table.

Property	Information
Molecular weight	236.7 ^a
Specific gravity	2.09 at 20°C/4°C ^a
Melting point	185°C (closed capillary) ^a
Boiling point	186°C at 777 mm Hg (sublimes) ^a
Log <i>K</i> _{ow}	4.14 ^a
Water solubility	50 mg/L at 25°C ^b
Vapor pressure	0.21 mm Hg at 20°C ^a
Vapor density relative to air	8.16 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

The applications of hexachloroethane have been extensive; however, industrial uses are diminishing. Hexachloroethane is used primarily in military smoke munitions (e.g., smoke pots, grenades, cartridges, and projectiles used to generate "smoke" or "fog") and in pyrotechnics.

The estimated average annual use of hexachloroethane from 1966 to 1977 at a major facility manufacturing smoke and pyrotechnic devices was 192,802 lb. In the 1970s, about half of the hexachloroethane distributed was used to manufacture military smoke-producing and pyrotechnic devices, 30% to 40% to manufacture degassing pellets to remove air bubbles from molten ore at aluminum foundries, and 10% to 20% as an antihelminthic to control liver flukes in sheep and cattle. The U.S. Food and Drug Administration withdrew approval for the use of hexachloroethane as an antihelminthic in 1971, and it probably is no longer used for this purpose (ATSDR 1997). Its use for degassing aluminum also has been almost completely phased out in the United States (EPA 1999). Other uses in metallurgy include refining alloys, removing impurities from molten metals, recovering metals from ores or smelting products, and as a degassing agent for magnesium; however, the European Union began phasing out the use of hexachloroethane in nonferrous metals in 1998 (EC 1998).

A number of other past uses of hexachloroethane have been identified, but many of these likely have been discontinued or involve the use of only limited quantities. Hexachloroethane is used as a laboratory chemical and as an ingredient in various fungicidal and insecticidal formulations, extreme-pressure lubricants, and plastics (ATSDR 1997, IARC 1999, HSDB 2009). Other past uses include as a moth repellent and in the chemical industry as a polymer additive, a plasticizer for cellulose esters, an accelerator, a vulcanizing agent, a process solvent in rubber manufacturing, a retardant in fermentation processes, and a component of submarine paints, and in the production of some types of synthetic diamonds. It has also been used as a component of fire-extinguishing fluids, an additive in combustible liquids (ignition suppressant), and an inhibitor of the explosiveness of methane and the combustion of ammonium perchlorate (IARC 1979, 1999, HSDB 2009).

Production

Production of hexachloroethane in the United States for commercial distribution began in 1921 and ended in 1967 (IARC 1979, ATSDR 1997). Currently, hexachloroethane is produced as a by-product of industrial chlorination of two-carbon hydrocarbons. It may be used in-house or recycled in feedstock to produce tetrachloroethylene or carbon tetrachloride. In 2009, hexachloroethane was produced by four manufacturers, all in India (SRI 2009) and was available from 35 suppliers, including 20 U.S. suppliers (ChemSources 2009). U.S. imports of hexachloroethane increased from 1.6 million pounds in 1976 to over 2 million pounds in 1977, 2.5 million pounds in 1985, and 4.5 million pounds in 1986 (ATSDR 1997). U.S. imports in the category of hexachloroethane and tetrachloroethane combined have shown an erratic pattern but have tended to decline in recent years, from 689,000 kg (1.5 million pounds) in 1989 to 139,000 kg (306,000 lb) in 2008 (USITC 2009). U.S. exports of hexachloroethane are not expected (ATSDR 1997). Exports in the category of hexachloroethane and tetrachloroethane combined reached a high of 11 million kilograms (25 million pounds) in 2005 and declined rapidly to 167,000 kg (368,000 lb) in 2008 (USITC 2009). Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of hexachloroethane totaled 10 million to 50 million pounds in 1986 and 1994, 1 million to 10 million pounds in 1990, 500,000 lb to 1 million pounds in 1998, and 10,000 to 500,000 lb in 2002 (EPA 2004). In 2006, the reported quantity was 1 million to 10 million pounds (EPA 2009).

Exposure

The routes of potential human exposure to hexachloroethane are inhalation, dermal contact, and ingestion (ATSDR 1997, NCI 1978).

The general population can be exposed to hexachloroethane in the environment at relatively low levels, primarily from ambient air but possibly also from drinking water (ATSDR 1997). According to EPA's Toxics Release Inventory, environmental releases of hexachloroethane from 1988 to 2007 ranged from a high of about 360,000 lb in 1994 to a low of 1,015 lb in 2004. These data, however, do not include releases at military facilities, which are exempt from reporting (TRI 2009). Although data on releases at military facilities are limited, a major military training facility in Fort Irwin, California, was reported to have released up to 6,683 kg (14,700 lb) of hexachloroethane from smoke devices from 1982 to 1984 (ATSDR 1997). In addition to releases to air from military uses, hexachloroethane may be released through combustion and incineration of chlorinated wastes, from hazardous waste sites, and in small amounts during chlorination of sewage effluent prior to discharge and during chlorination of raw water during drinking-water treatment.

Hexachloroethane is relatively persistent in the environment and has been detected in the atmosphere and in drinking water at low levels. When released to air, hexachloroethane is stable and is not expected to react with hydroxyl radicals or ozone (ATSDR 1997, HSDB 2009). Typical background atmospheric levels in the Northern Hemisphere ranged from 5 to 7 ppt (48 to 68 ng/m³). When released to surface water or soil, hexachloroethane is most likely to volatilize or to be adsorbed to soil or sediments; thus, it will have moderate to low mobility in soil. It has been detected in drinking-water wells near a toxic waste dump in Tennessee (median concentration = 0.26 µg/L). Hexachloroethane has also been detected at low levels in surface water, biota, ambient soil, sediments, and commercial food products (ATSDR 1997). Between 1977 and 1979, it was detected in 4 of 14 raw water samples from drinking-water supply sources. In 1975, it was measured in finished drinking water at a concentration of 4.4 µg/L (HSDB 2009). In the early 1980s, it was detected in only 1 of 882 ambient surface water samples and in none of 116 fish samples (based on data in EPA's STORET database). However, fish collected in Ohio in 1980 and 1981 contained hexachloroethane at a concentration of 0.1 mg/kg, and fish from Lake Michigan were reported to contain hexachloroethane, although concentrations were not reported (HSDB 2009). Some bioconcentration in fish has been reported; however, biomagnification through the food chain is unlikely, because hexachloroethane is rapidly metabolized by fish (ATSDR 1997).

Organochlorine pollutants, including hexachloroethane, were measured in human follicular fluid, serum, and seminal plasma in couples undergoing *in vitro* fertilization in Canada (Younglai *et al.* 2002). Hexachloroethane was found in over half of the samples of follicular fluid, at a mean concentration of 232 pg/mL.

Occupational exposure to hexachloroethane can occur through inhalation or dermal contact. Military and civilian personnel working with smoke or pyrotechnic devices that contain hexachloroethane could be exposed. Most of the hexachloroethane in a smoke pot or grenade is used up by the smoke-producing reaction, but small amounts (5% or less) remain after the smoke has formed and could result in further exposure. One study reported hexachloroethane concentrations in smoke ranging from 0.64 to 1.26 mg/m³. Plasma concentrations of hexachloroethane in workers exposed to hexachloroethane in loading and packing operations for smoke munitions production rose from 0.08 ± 0.14 µg/L to 7.3 ± 6.0 µg/L after more than five weeks of work in those areas, despite the use of protective equipment, including disposable overalls and compressed-air-fed visors or full-facepiece masks with filters (ATSDR 1997).

Other occupational exposure to hexachloroethane may occur during its manufacture, transportation, or use. Elevated amounts of hexachloroethane in the air can result when it is used in aluminum

foundries as a degassing agent. Industries that may have used hexachloroethane include real estate, paper and allied products, lumber and wood products, and amusement and recreation services (NIOSH 1978). Occupations with potential exposure to hexachloroethane include cleaners and charwomen, millwrights, miscellaneous machine operatives, plumbers and pipefitters, and electricians. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 8,516 workers, including 576 women, potentially were exposed to hexachloroethane in seven industries (Business Services; Machinery, Except Electrical; Chemicals and Allied Products; Primary Metal; Electric and Electronic Equipment; Transportation by Air; and Printing and Publishing) (NIOSH 1990).

Regulations

Department of Transportation (DOT)

Hexachloroethane is considered a hazardous substance, and special requirements have been set for transporting hexachloroethane in tank cars.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture of hexachloroethane is subject to certain provisions for the control of volatile organic compound emissions.

Clean Water Act

Effluent Guidelines: Listed as a toxic pollutant.

Water Quality Criteria: Based on fish and shellfish and water consumption = 1.4 µg/L; based on fish and shellfish consumption only = 3.3 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxicity characteristic leaching procedure (TCLP) threshold = 3.0 mg/L.

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of hexachloroethane = U131, F024, F025, K016, K030, K073.

Listed as a hazardous constituent of waste.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 1 ppm (10 mg/m³).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 1 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 1 ppm (10 mg/m³).

Immediately dangerous to life and health (IDLH) limit = 300 ppm.

Listed as a potential occupational carcinogen.

References

- Akron. 2009. *The Chemical Database*. The Department of Chemistry at the University of Akron. <http://uakron.edu/chem/chemdb/> and search on CAS number. Last accessed: 7/8/09.
- ATSDR. 1997. *Toxicological Profile for Hexachloroethane*. Agency for Toxic Substances and Disease Registry. <http://www.atsdr.cdc.gov/toxprofiles/tp97.html>.
- ChemIDplus. 2009. *ChemIDplus Advanced*. National Library of Medicine. <http://chem.sis.nlm.nih.gov/chemidplus/chemidheavy.jsp> and select Registry Number and search on CAS number. Last accessed: 7/8/09.
- ChemSources. 2009. *Chem Sources - Chemical Search*. Chemical Sources International. <http://www.chemsources.com/chemonline.html> and search on hexachloroethane. Last accessed: 7/8/09.
- EC. 1998. 98/241/EC: Council Decision of 23 March 1998 Concerning the Approval, on Behalf of the Community, of PARCOM Decision 96/1 on the Phasing-out of the Use of Hexachloroethane in the Non-ferrous Metal Industry. Europa. <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31998D0241:EN:NOT>. Last accessed: 9/22/10.
- EPA. 1999. *Comments Received from the Aluminum Association, February 25, 1999*. <http://74.125.93.132/search?q=cache%3AesIRF7KdTG4%3Awwww.epa.gov%2Fglno%2Fbnsdocs%2Focs%2Fcomments%2Falumass.pdf+Comments+Received+from+the+Aluminum+Association%2C+February+25%2C+1999&hl=en&gl=us>.

EPA. 2004. *Non-confidential IUR Production Volume Information*. U.S. Environmental Protection Agency. <http://www.epa.gov/oppt/iur/tools/data/2002-vol.html> and search on CAS number.

EPA. 2009. *Non-confidential 2006 IUR Records by Chemical, Including Manufacturing, Processing and Use Information*. U.S. Environmental Protection Agency. http://cfpub.epa.gov/iursearch/2006_iur_natlcheminfo.cfm?id=4243.

HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number. Last accessed: 7/8/09.

IARC. 1979. Hexachloroethane. In *Some Halogenated Hydrocarbons*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 20. Lyon, France: International Agency for Research on Cancer. pp. 467-476.

IARC. 1999. Hexachloroethane. In *Some Chemicals That Cause Tumors of the Kidney or Urinary Bladder in Rodents and Some Other Substances*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 73. Lyon, France: International Agency for Research on Cancer. pp. 295-306.

NCI. 1978. *Bioassay of Hexachloroethane for Possible Carcinogenicity*. NCI Technical Report Series no. 68. DHEW (NIH) Publication No. 78-1318. Bethesda, MD: National Cancer Institute. 106 pp.

NIOSH. 1978. *Current Intelligence Bulletin 27. Chloroethanes: Review of Toxicity*. National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/78181_27.html.

NIOSH. 1990. *National Occupational Exposure Survey (1981-83)*. National Institute for Occupational Safety and Health. Last updated: 7/1/90. <http://www.cdc.gov/noes/noes1/17385sic.html>.

NIOSH. 2005. Hexachloroethane. In *NIOSH Pocket Guide to Chemical Hazards*. National Institute for Occupational Safety and Health. Last updated: 9/05. <http://www.cdc.gov/niosh/npg/npgd0316.html>.

NTP. 1989. *Toxicology and Carcinogenesis Studies of Hexachloroethane (CAS No. 67-72-1) in F344/N Rats (Gavage Studies)*. NTP Technical Report Series no. 361. Research Triangle Park, NC: National Toxicology Program. 120 pp.

SRI. 2009. *Directory of Chemical Producers*. Menlo Park, CA: SRI Consulting. Database edition. Last accessed: 7/8/09.

TRI. 2009. *TRI Explorer Chemical Report*. U.S. Environmental Protection Agency. <http://www.epa.gov/triexplorer> and select Hexachloroethane. Last accessed: 7/8/09.

USITC. 2009. *USITC Interactive Tariff and Trade DataWeb*. United States International Trade Commission. http://dataweb.usitc.gov/scripts/user_set.asp and search on HTS no. 2903191000. Last accessed: 10/20/09.

Younglai EV, Foster WG, Hughes EG, Trim K, Jarrell JF. 2002. Levels of environmental contaminants in human follicular fluid, serum, and seminal plasma of couples undergoing *in vitro* fertilization. *Arch Environ Contam Toxicol* 43(1): 121-126.

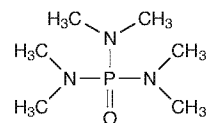
Hexamethylphosphoramide

CAS No. 680-31-9

Reasonably anticipated to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)

Also known as HMPA or hexamethylphosphoric triamide



Carcinogenicity

Hexamethylphosphoramide is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure of rats to hexamethylphosphoramide by inhalation caused nasal tumors, which are rare in this species. Inhalation of hexamethylphosphoramide caused benign and malignant nasal tumors (papilloma, epidermoid carcinoma, adenoid squamous carcinoma, transitional-cell carcinoma, and adenocarcinoma) in rats of both sexes (IARC 1977, Lee and Trochimowicz 1982).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to hexamethylphosphoramide.

Properties

Hexamethylphosphoramide is a phosphoric acid amide derivative that exists at room temperature as a colorless to light-amber mobile liquid with a spicy odor. It is miscible with water and most organic liquids but is immiscible with high-boiling-point saturated hydrocarbons. It is stable at normal temperatures and pressures (Akron 2009, HSDB 2009). Physical and chemical properties of hexamethylphosphoramide are listed in the following table.

Property	Information
Molecular weight	179.2 ^a
Specific gravity	1.03 at 20°C ^a
Freezing point	5°C to 7°C ^a
Boiling point	233°C at 760 mm Hg ^a
Log <i>K</i> _{ow}	0.28 ^b
Water solubility	1,000 g/L ^b
Vapor pressure	0.03 mm Hg at 25°C ^c
Vapor density relative to air	6.18 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009, ^cAkron 2009.

Use

Hexamethylphosphoramide was formerly used by its major U.S. producer only as a processing solvent for aromatic polyamide fiber (Kevlar); however, it now has a number of additional uses (IARC 1977, 1999, HSDB 2009). It is used as a solvent for other polymers, for gases, and for organic and organometallic reactions in research laboratories. It is also used as a polymerization catalyst, a stabilizer against thermal degradation in polystyrene, an additive to polyvinyl and polyolefin resins to protect against degradation by ultraviolet light, and a color-enhancing agent for the thiocyanate-cobalt complex used for cobalt detection. Hexamethylphosphoramide has been used as an antistatic agent and a flame retardant and deicing additive for jet fuels. It also can be used as a flame-retarding additive in lithium-ion batteries; however, it reduces the performance of the battery (Izquierdo-Gonzales *et al.* 2004).

Production

In 2009, hexamethylphosphoramide was produced by one manufacturer worldwide, in the United States (SRI 2009), and was available from 21 suppliers, including 14 U.S. suppliers (ChemSources 2009). No data on U.S. production, import, or export volumes were found.

Exposure

The routes of potential human exposure to hexamethylphosphoramide are inhalation, ingestion, and dermal contact (HSDB 2009). The major source of exposure is probably occupational; however, the general population potentially could be exposed through release of hexamethylphosphoramide to the environment. No environmental releases of hexamethylphosphoramide were reported in the U.S. Environmental Protection Agency's Toxics Release Inventory (TRI 2009). Hexamethylphosphoramide exists in the air solely in the vapor phase and will be degraded by photochemically produced hydroxyl radicals, with a half-life of 2 hours (HSDB 2009). If released to soil or water, hexamethylphosphoramide may leach rapidly in soil and sediments. It is not expected to bioconcentrate in aquatic organisms.

EPA evaluated the potential for release of hexamethylphosphoramide into the soil, surface water, and groundwater near a site in Spruance, Virginia, where hexamethylphosphoramide was used and disposed of (EPA 1980, 1999). In 1976, disposal of hexamethylphosphoramide from the facility directly into the James River was documented. Up to 48 lb per month was discharged; however, surface-water concentrations downstream from the discharge point

were approximately 0.5 ppb, the lower limit of detection. Solid wastes from the Spruance site containing hexamethylphosphoramide also had been disposed of in Anniston, Alabama; evaluation of the disposal site indicated detectable quantities of hexamethylphosphoramide in a drainage ditch downstream from the disposal site, in an on-site groundwater well, and in a well upgradient from the disposal site, but not in Anniston's drinking water. The waste was removed from the disposal site, and remedial actions were taken at the site to mitigate risks of human exposure (EPA 1980). In 1999, hexamethylphosphoramide was identified as a contaminant in groundwater monitoring wells at the Spruance facility site, in nearby off-site wells at concentrations of up to 480 µg/L, and in surface water downgradient from the facility at a concentration of 0.17 µg/L (EPA 1999). Potential levels of off-site exposure were below levels of concern for human health and the environment.

Occupational exposure may occur among workers involved in the production of hexamethylphosphoramide or in its use as a solvent or chemical additive or in the packaging of consumer products. The National Institute for Occupational Safety and Health estimated that up to 90% of about 5,000 people who worked in U.S. laboratories that used hexamethylphosphoramide might have been exposed (NIOSH 1975). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 700 workers (in the Business Services industry), including 51 women, potentially were exposed to hexamethylphosphoramide (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

Hexamethylphosphoramide is listed as a potential occupational carcinogen.

References

- Akron. 2009. *The Chemical Database*. The Department of Chemistry at the University of Akron. <http://ull.chemistry.uakron.edu/erd> and search on CAS number. Last accessed: 4/29/09.
- ChemIDplus. 2009. *ChemIDplus Advanced*. National Library of Medicine. <http://chem.sis.nlm.nih.gov/chemidplus/chemidheavy.jsp> and select Registry Number and search on CAS number. Last accessed: 5/11/09.
- ChemSources. 2009. *Chem Sources - Chemical Search*. Chemical Sources International. <http://www.chemsources.com/chemonline.html> and search on hexamethylphosphoramide. Last accessed: 4/29/09.
- EPA. 1980. *Chemical Hazard Information Profiles (CHIPs), August 1976 – August 1978*. EPA 560/11-80-011. Washington, DC: U.S. Environmental Protection Agency. pp. 142-146.
- EPA. 1999. *Environmental Indicator (EI) RCRIIS code (CA750) – Migration of Contaminated Groundwater Under Control, DuPont Spruance Environmental Indicator Form*. U.S. Environmental Protection Agency. http://www.epa.gov/reg3wcmd/ca/va/gwpdf/gw_vad009305137.pdf.
- HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number. Last accessed: 4/29/09.
- IARC. 1977. Hexamethylphosphoramide. In *Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 15. Lyon, France: International Agency for Research on Cancer. pp. 211-222.
- IARC. 1999. Hexamethylphosphoramide. In *Re-evaluation of Some Organic Chemicals, Hydrazine, and Hydrogen Peroxide*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 71. Lyon, France: International Agency for Research on Cancer. pp. 1465-1481.
- Izquierdo-Gonzales S, Li W, Lucht BL. 2004. Hexamethylphosphoramide as a flame retarding additive for lithium-ion battery electrolytes. *J Power Sources* 135(1-2): 291-296.
- Lee KP, Trochimowicz HJ. 1982. Induction of nasal tumors in rats exposed to hexamethylphosphoramide by inhalation. *J Natl Cancer Inst* 68(1): 157-171.

NIOSH. 1975. *Current Intelligence Bulletin 6. Hexamethylphosphoric Triamide (HMPA)*. National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/78127_6.html.

NIOSH. 1990. *National Occupational Exposure Survey (1981-83)*. National Institute for Occupational Safety and Health. Last updated: 7/1/90. <http://www.cdc.gov/noes/noes1/x4066sic.html>.

SRI. 2009. *Directory of Chemical Producers*. Menlo Park, CA: SRI Consulting. Database edition. Last accessed: 4/29/09.

TRI. 2009. *TRI Explorer Chemical Report*. U.S. Environmental Protection Agency. <http://www.epa.gov/triexplorer> and select Hexamethylphosphoramide. Last accessed: 4/29/09.

Human Papillomaviruses: Some Genital-Mucosal Types

CAS No.: none assigned

Known to be human carcinogens

First listed in the *Eleventh Report on Carcinogens* (2004)

Also known as HPVs

Carcinogenicity

Some human papillomaviruses (HPVs) of the genital-mucosal type are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

In epidemiological research, numerous case-control studies have consistently reported strong associations between cervical cancer and infection with HPV-16, HPV-18, or "high-risk" HPVs as a class (discussed under Properties, below). Moreover, several case-control studies have provided strong evidence of positive associations between cervical cancer and other individual HPVs, including HPV types 31, 33, 35, 39, 45, 51, 52, 58, and 59 (Muñoz 2000). Cohort studies have demonstrated that infection with HPV-16 or with high-risk HPVs as a class occurs before the development of high-grade cervical intraepithelial neoplasia (CIN), which is thought to be a precursor of invasive cancer. The evidence from cohort studies is weaker for individual high-risk viruses, possibly because they are less common; among these, the evidence for an association with cervical cancer appears to be strongest for HPV-18 (NTP 2003). It is unlikely that the association between HPV infection and cervical cancer is due to other factors that could increase the risk of cancer, because many studies included these factors in their analysis, and because of the large magnitude of the odds ratios estimated in the case-control studies. Thus, these studies demonstrate that some genital-mucosal HPVs cause cervical cancer. In addition to the association with cervical cancer, there is strong evidence that HPV-16 infection is associated with other anogenital cancers, especially cancer of the vulva (NTP 2003). Evidence also suggests associations between HPV infection and some cancers of the head and neck and, especially, the soft palate (oropharynx), tonsils, and back of the tongue and throat (NTP 2003).

Based on testing of tissue specimens from more than 1,000 invasive malignant cervical tumors from women from 22 countries (collected for the International Biological Study of Cervical Cancer), it was estimated that HPV is present in 99.7% of all malignant cervical tumors, suggesting that HPV infection may be necessary for development of cervical cancer (Walboomers *et al.* 1999). Nonetheless, not all individuals infected with HPV develop cervical cancer. Most HPV infections (about 70%) clear within 1 to 2 years, and thus confer little risk of cancer. The specific risk factor for cervical cancer appears to be persistent infection with HPV-16 or other high-risk HPVs. Whether HPV infections persist probably depends both on viral characteristics, such as greater persistence of specific HPV types or variants, and on characteristics of the patient, such as sex-hormone levels, smoking behavior, or immune-system status.

Since human papillomaviruses (some genital-mucosal types) were listed in the *Eleventh Report on Carcinogens*, numerous human cancer studies on HPVs have been published. The International Agency for Research on Cancer concluded that HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66 were carcinogenic in humans based on sufficient evidence for the carcinogenicity of HPV-16 in the cervix, vulva, vagina, penis, anus, oral cavity, and oropharynx and sufficient evidence for the carcinogenicity of HPV types 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66 in the cervix. IARC also concluded that there was limited evidence for the carcinogenicity of HPV types 6, 11, and 18 in the vulva, penis, and anus; HPV types 6, 11, 16, and 18 in the larynx; HPV-18 in the vagina; and HPV-16 in the periungual skin (the skin around the fingernails or toenails) (IARC 2007).

Cancer Studies in Experimental Animals

Because HPV infections are specific to humans, experimental animals cannot be infected with them. Many studies have investigated the carcinogenicity of various animal papillomaviruses both in their natural host species and in other species. Studies in monkeys, cattle, rabbits, and sheep have shown that animal papillomaviruses cause cancer in their natural hosts. Studies in transgenic mice carrying HPV genes demonstrated that HPV proteins play a role in the development of abnormal tissue growth (dysplasia) and progression to tumor formation. Transgenic mice expressing some HPV type 16 or 18 genes and producing the corresponding viral proteins developed tumors of the cervix and other tissues (Arbeit *et al.* 1994, Comerford *et al.* 1995).

Studies on Mechanisms of Carcinogenesis

Infection with high-risk HPVs is associated with chromosomal aberrations, including abnormal centrosome numbers, chromosomal imbalances at specific chromosomal regions, and changes in chromosome number, including tetrasomy and other types of aneuploidy (NTP 2003).

HPV can integrate into the DNA of the host cell and can immortalize and transform cells, enabling them to proliferate and form tumors. Most studies on the mechanisms of HPV carcinogenesis have investigated HPV-16 and HPV-18. HPV types 16, 18, 31, and 33 have been shown to transform cells, types 16, 18, and 31 to immortalize cells, and types 16 and 18 to produce proteins that bind to regulatory proteins of the host cell. The HPV proteins E2 and E5 and the long control region of the HPV genome (discussed under Properties, below) play a role in HPV-induced cell transformation. However, the HPV proteins primarily responsible for immortalization and transformation are E6 and E7, as shown in studies with human and rodent cell cultures. Studies with transgenic mice expressing the E6 or E7 gene further support the notion that the E6 and E7 proteins are important in HPV-associated neoplasia. Both the E6 and E7 proteins alter the pathways that regulate tissue growth, by interfering with growth receptors or growth factors; production of cytokines has been shown to be altered in cells infected with HPV-16. The E6 protein increases degradation of the p53 tumor-suppressor protein, thereby interfering with apoptosis. The E7 protein disrupts complexes of the transcription factor E2F with the tumor-suppressor protein pRb and related proteins involved in control of the cell cycle and causes their degradation, altering control of transcription and progression of the cell cycle. The E7 protein has been shown to cause abnormal synthesis and duplication of centrosomes, resulting in abnormal mitotic division.

Properties

HPVs of the genital-mucosal type are DNA viruses that infect the genital skin and genital and non-genital mucosa, sometimes causing genital warts or cervical abnormalities. They are members of the family

Papillomaviridae, which consists of species-specific non-enveloped viruses that infect the squamous epithelium of the skin and mucosal membranes of animals. More than 100 different HPVs had been identified by 2004, including viruses that cause skin warts as well as the genital-mucosal type (Howley and Lowy 2001). The over 40 genital-mucosal HPVs have been classified as either “high risk” or “low risk”; high-risk viruses have been associated with cervical cancer in human epidemiological studies, whereas low-risk viruses have been associated with genital warts or low-grade CIN (abnormal tissue growth in the cervical epithelium that is unlikely to progress to cancer). Most studies have considered HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68 to be high-risk viruses; some studies also include other HPVs, most notably HPV-66. Classification of HPVs is based also on phylogenetic and mechanistic considerations. Most high-risk viruses have DNA sequences highly similar to those of either HPV-16 or HPV-18, suggesting that they are closely related to these types. Studies on the mechanisms of carcinogenesis have shown that high-risk but not low-risk viruses immortalize human keratinocytes (skin cells), interact with the tumor-suppressor proteins pRb and p53, and cause chromosomal aberrations. However, most mechanistic studies have evaluated only a few HPVs, the majority focusing on HPV-16 or HPV-18 and a few on HPV-31 or HPV-33.

HPVs are small (about 52 to 55 nm in diameter), consisting of about 8,000 base pairs of covalently closed, double-stranded DNA. The viral genome consists of a series of open reading frames, each of which is a DNA sequence that codes for an HPV protein, and a long control region, which contains elements that regulate DNA replication and protein synthesis. Productive infection of cells (leading to replication of the virus) is linked to their stages of differentiation. Viral replication can be divided into early and late stages, which occur in cells at different stages of differentiation. Early stages of replication (including attachment of the virus to the cell, entry and uncoating, early gene expression, protein production, and DNA replication) occur in basal cells. These cells are the youngest, least differentiated cells and are located in the lower layers of the epithelium; they are the only dividing cells in the squamous epithelium. Late stages of viral replication, which include the events leading to production of viral particles (late gene expression, production of capsid proteins, vegetative viral DNA replication, and virus assembly and release), occur in the terminally differentiating squamous epithelial cells, which are the oldest, most differentiated cells, in the upper layers of the epithelium. The genes expressed in the early stages of viral replication, designated E1 through E8, are associated with regulation of transcription (e.g., E2) and cellular proliferation (e.g., E6 and E7). The genes expressed in the late stages, designated L1 and L2, encode the two proteins that make up the viral capsid (Howley and Lowy 2001).

Infection, Prevention, and Treatment

Genital-mucosal HPVs infect the cervix, causing lesions of varying severity, including genital warts, low- and high-grade CIN, and invasive cervical cancer (Einstein and Burk 2001). Low-grade CIN (CIN I) is a well-differentiated lesion in which the squamous epithelial cells show alterations characteristic of the cytopathogenic effects of a replicative viral infection, such as the presence of two nuclei or other nuclear abnormalities and koilocytosis (the presence of cells with abnormal nuclei and a hollow appearance resulting from collapse of the cell's internal structure). The alterations seen in CIN I are not usually considered to be precursors of cancer. The majority of CIN I lesions are transient and resolve spontaneously, but a small percentage may progress to high-grade CIN or invasive cancer (Jastreboff and Cymet 2002). Both high-risk and low-risk HPVs can cause low-grade CIN (IARC 1995). High-grade CIN (CIN II or III) is characterized by the

presence of undifferentiated cells above the lower third of the epithelium (extending into the upper layers) and by nuclear crowding, substantial pleomorphism, loss of tissue organization and cellular polarity, abnormal mitotic figures, and larger numbers of atypical cells than observed in low-grade CIN (IARC 1995). High-grade CIN probably results from persistent HPV infection, and it is more likely than low-grade CIN to progress to invasive cancer. (CIN III is also known as carcinoma *in situ*, or noninvasive cancer.) Microinvasive squamous-cell cervical cancer usually arises from high-grade CIN.

Two HPV vaccines are licensed by the U.S. Food and Drug Administration and recommended by the Centers for Disease Control and Prevention (CDC 2010). Both vaccines are effective against HPV types 16 and 18, which are responsible for most cervical cancer, and one of the vaccines is also effective against HPV 6 and 11, which cause genital warts. Both vaccines are given in three doses, with the second dose given one to two months after the first and the third dose six months after the first (CDC 2009). Treatment of HPV infection depends on the severity of the disease and may involve topical applications, interferon-related therapies, or excision of the lesion via laser methods, surgery, or cryotherapy.

Detection

HPV infection is detected by observation of visible lesions or microscopic changes in cells, by detection of HPV DNA, or by detection of antibodies against HPV proteins in the blood. Genital warts (condylomata acuminata) are genital lesions visible to the naked eye; they have a fleshy red appearance and a raised surface that usually extends in papillae. Flat condylomata are flat, nonpapillary lesions; they are more difficult to detect and may be apparent only after swabbing with acetic acid and colposcopic examination, in which they appear as white, flat, shiny lesions. The Papanicolaou (Pap) smear, which involves microscopic examination of stained exfoliated genital cells, detects koilocytosis and other signs of CIN; it is used to screen for cervical cancer by detecting high-grade CIN (Trofatter 1997).

The most sensitive and specific method for detecting HPV infection is to test for HPV DNA. DNA testing can be used to detect a broad spectrum of HPV genotypes (Trofatter 1997). Detection of HPV DNA signifies present exposure or persistent infection resulting from a past exposure. The most sensitive HPV DNA tests are (1) those based on the polymerase chain reaction and (2) the Hybrid Capture assay, which is based on the formation of hybrids between HPV DNA and RNA probes. The most commonly used serological tests for HPV infection measure antibodies (immunoglobulin G) against capsid antigens (most often tested as virus-like particles). Several validation studies have estimated the sensitivity of such serological tests to be approximately 50%, using detection of HPV DNA as a standard (Dillner 2000). Because of their low sensitivity, serological assays are not recommended for diagnostic use, but they are useful for comparison of groups in epidemiological studies, which also commonly use HPV DNA testing. Clinical diagnosis of HPV is most commonly based on the Hybrid Capture 2 assay.

Exposure

Genital-mucosal HPVs are transmitted primarily through sexual contact with infected cervical, vaginal, vulvar, penile, or anal epithelium (IARC 1995). This finding is supported by numerous epidemiological studies demonstrating that HPV infection is associated with behaviors related to sexual activity. Numerous studies of HPV in women have reported a positive association between lifetime number of sex partners and HPV seropositivity (Sun *et al.* 1999, Silins *et al.* 2000) or the presence of HPV DNA (Franco *et al.* 1995, Kjør *et al.* 1997, Lazcano-Ponce *et al.* 2001). Recent sexual activity, the number of sex partners,

frequency of sexual intercourse, and presence of genital warts on sex partners are strong predictors of HPV infection, as indicated by HPV DNA testing (Franco *et al.* 1995, Ho *et al.* 1998). The role of men in carrying HPV infection from one woman to another has been demonstrated in studies showing that cervical cancer is relatively more frequent among wives whose husbands have detectable HPV DNA in their penis or whose husbands have had more extramarital partners (Bosch *et al.* 1996). Penile lesions containing the DNA of high-risk HPVs are frequent among male sex partners of women with CIN (Bleeker *et al.* 2002). There are conflicting reports as to whether HPV is transmitted at birth or perinatally. Infants exposed perinatally to HPV-11, or less commonly to HPV-6, may develop a rare benign tumor of the airway called juvenile-onset recurrent respiratory papillomatosis (Shoultz *et al.* 1997).

HPV infection is one of the most common sexually transmitted diseases. It appears that the majority of those infected have no symptoms, and it is estimated that 20 million people in the United States are infected with HPV (CDC 2001). The percentage of infected individuals (prevalence) is highest among those who are young and sexually active. U.S. epidemiological studies based on HPV DNA testing indicate that between 25% and 40% of sexually active women aged 15 to 25 are infected (Lowy and Howley 2001). Among all U.S. men and women aged 15 to 49, the estimated prevalence of HPV infection (based on HPV DNA testing) is 10% to 20%, whereas only 1% have genital warts, and 4% show cellular abnormalities associated with HPV infection (Koutsky 1997). For most populations of mixed age groups, the prevalence of HPV infection has been estimated at 5% to 15%. HPV-16 appears to be the most prevalent type worldwide (Jastreboff and Cymet 2002). In a study of women aged 18 to 40 with no history of high-grade CIN, among whom the prevalence of HPV was 39%, high-risk HPVs were more common (occurring in 26.7% of women) than low-risk HPVs (occurring in 14.7%) (Peyton *et al.* 2001).

In 2000, CDC estimated the number of new genital HPV cases per year (incidence) to be 5.5 million (CDC 2001). In the general population of Rochester, Minnesota, the average age- and gender-adjusted incidence of genital warts increased from 13 per 100,000 in the early 1950s to 106 per 100,000 in the late 1970s. During this period, the U.S. incidence of other sexually transmitted diseases also increased dramatically (IARC 1995, Shoultz *et al.* 1997). Several follow-up studies reported very high incidences of HPV infection (as detected by HPV DNA testing) among young, sexually active individuals, with three-year cumulative incidences ranging from 43% to 55% (Ho *et al.* 1998, Moscicki *et al.* 2001).

In most women infected with HPV (70%), the infection clears within 12 to 24 months (Franco *et al.* 1999, Dillner 2000). Some studies have suggested that low-risk HPV infections are more likely to regress than are high-risk HPV infections (Franco *et al.* 1999, Elfgren *et al.* 2000). The immune system plays an important role in HPV infection; immunocompromised patients are at increased risk for persistent HPV infection (Lowy and Howley 2001).

Regulations

No specific regulations or guidelines relevant to reduction of exposure to HPVs were identified.

References

- Arbeit JM, Münger K, Howley PM, Hanahan D. 1994. Progressive squamous epithelial neoplasia in K14-human papillomavirus type 16 transgenic mice. *J Virol* 68(7): 4358-4368.
- Bleeker MC, Hogewoning CJ, Van Den Brule AJ, Voorhorst FJ, Van Andel RE, Risse EK, Starink TM, Meijer CJ. 2002. Penile lesions and human papillomavirus in male sexual partners of women with cervical intraepithelial neoplasia. *J Am Acad Dermatol* 47(3): 351-357.

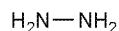
- Bosch FX, Castellsague X, Munoz N, de Sanjose S, Gaffari AM, Gonzalez LC, *et al.* 1996. Male sexual behavior and human papillomavirus DNA: key risk factors for cervical cancer in Spain. *J Natl Cancer Inst* 88(15): 1060-1067.
- CDC. 2001. *Tracking the Hidden Epidemics 2000: Trends in STDs in the United States*. Centers for Disease Control and Prevention. <http://www.cdc.gov/std/trends2000/Trends2000.pdf>.
- CDC. 2009. *HPV Vaccine—Questions & Answers*. Centers for Disease Control and Prevention. Last updated 12/22/09. <http://www.cdc.gov/vaccines/vpd-vac/hpv/vac-faqs.htm>.
- Comerford SA, Maika SD, Laimins LA, Messing A, Elsasser HP, Hammer RE. 1995. E6 and E7 expression from the HPV 18 LCR: development of genital hyperplasia and neoplasia in transgenic mice. *Oncogene* 10(3): 587-597.
- Dillner J. 2000. Trends over time in the incidence of cervical neoplasia in comparison to trends over time in human papillomavirus infection. *J Clin Virol* 19(1-2): 7-23.
- Einstein MH, Burk RD. 2001. Persistent human papillomavirus infection: definitions and clinical implications. *Papillomavirus Report* 12: 119-123.
- Elfgren K, Kalantari M, Moberger B, Hagmar B, Dillner J. 2000. A population-based five-year follow-up study of cervical human papillomavirus infection. *Am J Obstet Gynecol* 183(3): 561-567.
- Franco EL, Villa LL, Ruiz A, Costa MC. 1995. Transmission of cervical human papillomavirus infection by sexual activity: differences between low and high oncogenic risk types. *J Infect Dis* 172(3): 756-763.
- Franco EL, Villa LL, Sobrinho JP, Prado JM, Rousseau MC, Desy M, Rohan TE. 1999. Epidemiology of acquisition and clearance of cervical human papillomavirus infection in women from a high-risk area for cervical cancer. *J Infect Dis* 180(5): 1415-1423.
- Ho GY, Bierman R, Beardsley L, Chang CJ, Burk RD. 1998. Natural history of cervicovaginal papillomavirus infection in young women. *N Engl J Med* 338(7): 423-428.
- Howley PM, Lowy DR. 2001. Papillomaviruses and their replication. In *Fields' Virology*. Knipe DM, Howley PM, eds. Philadelphia: Lippincott Williams & Wilkins. pp. 2197-2229.
- IARC. 1995. *Human Papillomaviruses*. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 64. Lyon, France: International Agency for Research on Cancer. 409 pp.
- IARC. 2007. *Human Papillomaviruses*. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 90. Lyon, France: International Agency for Research on Cancer. 670 pp.
- Jastreboff AM, Cymet T. 2002. Role of the human papilloma virus in the development of cervical intraepithelial neoplasia and malignancy. *Postgrad Med J* 78(918): 225-228.
- Kjær SK, van den Brule AJ, Bock JE, Poll PA, Engholm G, Sherman ME, Walboomers JM, Meijer CJ. 1997. Determinants for genital human papillomavirus (HPV) infection in 1000 randomly chosen young Danish women with normal Pap smear: are there different risk profiles for oncogenic and nononcogenic HPV types? *Cancer Epidemiol Biomarkers Prev* 6(10): 799-805.
- Koutsky L. 1997. Epidemiology of genital human papillomavirus infection. *Am J Med* 102(5A): 3-8.
- Lazcano-Ponce E, Herrero R, Muñoz N, Cruz A, Shah KV, Alonso P, Hernández P, Salmerón J, Hernández M. 2001. Epidemiology of HPV infection among Mexican women with normal cervical cytology. *Int J Cancer* 91(3): 412-420.
- Lowy DR, Howley PM. 2001. Papillomaviruses. In *Fields' Virology*. Knipe DM, Howley PM, eds. Philadelphia, PA: Lippincott Williams & Wilkins. pp. 2231-2264.
- Moscicki AB, Hills N, Shiboski S, Powell K, Jay N, Hanson E, *et al.* 2001. Risks for incident human papillomavirus infection and low-grade squamous intraepithelial lesion development in young females. *JAMA* 285(23): 2995-3002.
- Munoz N. 2000. Human papillomavirus and cancer: the epidemiological evidence. *J Clin Virol* 19(1-2): 1-5.
- NTP. 2003. *Report on Carcinogens Background Document for Human Papillomaviruses: Genital-Mucosal Types*. National Toxicology Program. http://ntp.niehs.nih.gov/ntp/newhomeroc/roc11/HPV_RG2_Public.pdf.
- Peyton, CL, Gravitt PE, Hunt WC, Hundley RS, Zhao M, Apple RJ, Wheeler CM. 2001. Determinants of genital human papillomavirus detection in a US population. *J Infect Dis* 183(11): 1554-1564.
- Shoultz DA, Koutsky LA, Galloway DA. 1997. Epidemiology and modes of transmission. In *Human Papillomavirus Infections in Dermatovenereology*. Gross G, von Krogh G, eds. Boca Raton, FL: CRC Press. pp. 83-97.
- Silins I, Kallings I, Dillner J. 2000. Correlates of the spread of human papillomavirus infection. *Cancer Epidemiol Biomarkers Prev* 9(9): 953-959.
- Sun Y, Eluf-Neto J, Bosch FX, Munoz N, Walboomers JM, Meijer CJ, Shah KV, Clayman B, Viscidi RP. 1999. Serum antibodies to human papillomavirus 16 proteins in women from Brazil with invasive cervical carcinoma. *Cancer Epidemiol Biomarkers Prev* 8(10): 935-940.
- Trofatter KF. 1997. Diagnosis of human papillomavirus genital tract infection. *Am J Med* 102(5A): 21-27.
- Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, *et al.* 1999. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 189(1): 12-19.

Hydrazine and Hydrazine Sulfate

CAS Nos. 302-01-2 and 10034-93-2

Reasonably anticipated to be human carcinogens

First listed in the *Third Annual Report on Carcinogens* (1983)



Carcinogenicity

Hydrazine and hydrazine sulfate are *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure to hydrazine or hydrazine sulfate caused tumors in two rodent species at several different tissue sites and by several different routes of administration. Most studies of oral exposure used hydrazine sulfate. Oral exposure to hydrazine sulfate (either in the drinking water or by stomach tube) caused benign and malignant lung tumors (adenoma and adenocarcinoma) in mice and rats of both sexes and liver cancer in mice of both sexes (hepatocellular carcinoma) and in male rats (spindle-cell sarcoma). Intraperitoneal injection of hydrazine caused lung tumors, myeloid leukemia, and lymphoma (reticulum-cell sarcoma) in mice of both sexes (IARC 1974).

Since hydrazine and hydrazine sulfate were listed in the *Third Annual Report on Carcinogens*, additional studies in rodents have been identified. Perinatal exposure to hydrazine sulfate caused lung cancer (adenocarcinoma) in mice as adults (IARC 1987). Exposure to hydrazine by inhalation caused benign or malignant nasal tumors (adenomatous or villous polyps, adenocarcinoma, or squamous-cell papilloma or carcinoma) in rats and benign tumors of the nasal cavity (adenomatous polyps) in male hamsters. A few tumors of the colon (adenocarcinoma, leiomyoma, and papilloma) and thyroid (parafollicular-cell adenoma) also were observed in male hamsters at the highest exposure level and may have been exposure-related (Vernot *et al.* 1985, IARC 1987). Administration of hydrazine sulfate in the drinking water caused liver cancer (hepatocellular carcinoma) in hamsters (IARC 1999).

Cancer Studies in Humans

No excess risk of cancer was found in a small cohort study of 423 men engaged in the manufacture of hydrazine (Roe 1978). Since hydrazine and hydrazine sulfate were listed in the *Third Annual Report on Carcinogens*, additional epidemiological studies have been identified. The International Agency for Research on Cancer concluded in 1999 that the evidence for the carcinogenicity of hydrazine from studies in humans was inadequate. No excess risk of cancer mortality was found in a follow-up of the Roe cohort (Wald *et al.* 1984, Wald 1985) or in a small retrospective cohort study of 427 workers in a hydrazine plant (Morris *et al.* 1995). Since the 1999 IARC review, studies of two additional cohorts have been identified. A significant dose-response relationship between hydrazine exposure and lung-cancer incidence and mortality and a significant increase in colorectal-cancer incidence were found among aerospace workers, of whom about one fourth potentially were exposed to hydrazine, 1-methylhydrazine, or 1,1-dimethylhydrazine in rocket fuel (Ritz *et al.* 1999, 2006). No association between smoking and hydrazine exposure was observed for a subset of these workers, and risk estimates were adjusted for potentially confounding occupational exposures. No significant association between cancer mortality and potential exposure to hydrazine was found in a retrospective cohort study of workers at a rocket en-

gine testing facility, of whom 315 likely had been exposed to hydrazines (Boice Jr. *et al.* 2006).

Properties

At room temperature, hydrazine is a colorless oily liquid with a penetrating ammonia-like odor, and hydrazine sulfate is a white crystalline solid (HSDB 2009). Hydrazine is miscible with methyl, ethyl, propyl, and butyl alcohols, slightly miscible with hydrocarbons and halogenated hydrocarbons, and insoluble in chloroform and ether. Hydrazine sulfate is soluble in water but practically insoluble in ethanol. Both compounds are thermally unstable (Akron 2009). Physical and chemical properties of hydrazine and hydrazine sulfate are listed in the following table.

Property	Hydrazine	Hydrazine Sulfate
Molecular weight	32.1	130.1
Specific gravity	1.0036 at 25°C/4°C	1.378
Melting point	2.0°C	254°C
Boiling point	113.5°C at 760 mm Hg	NR
Log K_{ow}	-2.07	NR
Water solubility	1,000 g/L	34.1 g/L
Vapor pressure	14.4 mm Hg at 25°C	NR
Dissociation constant (pK_a)	7.96	6.7

Source: HSDB 2009. NR = Not reported.

Use

Hydrazine is used primarily as a chemical intermediate to produce agricultural chemicals and chemical blowing agents, as a corrosion inhibitor and water-treatment chemical, and as a rocket propellant. In the early 1980s, 40% of hydrazine was used in agricultural chemicals, 33% in blowing agents, 15% as a corrosion inhibitor, and 5% as a rocket propellant (ATSDR 1997). It has been used for plating metals on glass and plastics, in fuel cells and solder fluxes, as a reducing agent in electrode-less nickel plating, as a chain extender in urethane polymerizations, and as a reducing agent in extraction of plutonium from nuclear reactor waste. It has also been used to produce photography chemicals, textile dyes, heat stabilizers, explosives, hydrazine sulfate, and antituberculars and other pharmaceuticals (Sax and Lewis 1987, ATSDR 1997, HSDB 2009).

Hydrazine sulfate has been used in refining rare metals, as an antioxidant in soldering flux for light metals, in analytical tests for blood, as a reducing agent in the analysis of minerals and slag, in the preparation of hydrazine hydrate, in the manufacture of chemicals, in condensation reactions, as a catalyst in making acetate fibers, as a fungicide and germicide, in the analysis of minerals, and in the determination of arsenic in metals (HSDB 2009b).

Production

U.S. production capacity for hydrazine hydrate was estimated at 55 million pounds in 1988, and production capacity for hydrazine solutions was 36.3 million pounds in 1992 (IARC 1999). In 2009, hydrazine was produced by three manufacturers worldwide, including one in the United States, and hydrazine sulfate by 14 manufacturers, including one in the United States (SRI 2009). Hydrazine was available from 27 suppliers, including 19 U.S. suppliers, and hydrazine sulfate from 34 suppliers, including 20 U.S. suppliers (ChemSources 2009). U.S. imports in the category "hydrazine and hydroxylamine and their salts" generally increased from 1989 to 2008, reaching a low of 2 million kilograms (4.4 million pounds) in 1993 and a high of 23.5 million kilograms (51.8 million pounds) in 1999 (USITC 2009). During this period, U.S. exports in this category fluctuated but generally declined, from a high of 20.3 million kilograms (44.7 million pounds) in 1997 to a low of 2.4 million kilograms (5.3 million pounds)

in 2008. Reports filed in 1986 and 1990 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of hydrazine totaled 10,000 to 500,000 lb. No reports for hydrazine were filed in 1994 or 1998, but reports filed in 2002 and 2006 indicated quantities of 1 million to 10 million pounds (EPA 2004, 2009). Inventory update reports were filed for hydrazine sulfate only in 1990, indicating a total quantity of 10,000 to 500,000 lb (EPA 2004).

Exposure

The primary routes of potential human exposure to hydrazine are ingestion, inhalation, and dermal contact (HSDB 2009). The exposure potential for the general population is low, but exposure may occur through inhalation of cigarette smoke or ingestion of trace amounts in processed foods. Hydrazine has been detected in cigarette smoke at a concentration of 32 µg per cigarette (PHS 1982). Hydrazine sulfate may be ingested intentionally, as it has been studied as a treatment for cancer (NCI 2008).

Hydrazine and hydrazine sulfate may be released to the environment through production, use, and waste disposal (ATSDR 1997, HSDB 2009). EPA's Toxics Release Inventory reported that in 2007, environmental releases of hydrazine from 23 facilities totaled 16,759 lb, 14,570 lb of which was released by one facility to underground injection wells. Releases of hydrazine sulfate between 1988 and 2003 ranged from 24,000 lb (in 2001) to 356,172 lb (in 1988), with no major long-term trend. Almost all hydrazine sulfate was released to underground injection wells; a small amount was released to air. No releases of hydrazine sulfate were reported after 2003 (TRI 2009). In most environmental media, hydrazine is rapidly degraded by oxidation. High concentrations of hydrazine are toxic to microorganisms, but at low concentrations, biodegradation may occur. Use of hydrazine in boiler water treatment may result in its brief occurrence in discharged waste, where it will be oxidized (ATSDR 1997, HSDB 2009).

Occupational exposure is most likely to occur by inhalation or dermal contact where hydrazine or hydrazine sulfate is produced or used (HSDB 2009). Hydrazine exposure has been documented in the paper, tire-manufacturing, military, and aerospace industries (Helmert *et al.* 2004, Korhonen *et al.* 2004, Ritz *et al.* 2006, Durmusoglu *et al.* 2007). In the vulcanization step of tire manufacturing, hydrazine was measured at concentrations of up to 8.0 mg/m³, resulting in an estimated daily intake of 0.0031 mg/kg of body weight (Durmugoglu 2007). Hydrazine fuels are used for rockets and high-performance military jet aircraft; exposure of workers refueling these planes has been reported (Helmert 2004). The National Aeronautics and Space Administration reported developing a reusable propellant-handler's suit that was expected to be the world's most advanced garment for protection from chemical agents, especially rocket propellants such as hydrazine (Doerr 2001). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 60,490 workers, including 2,841 women, potentially were exposed to hydrazine and that 14,330 workers, including 6,716 women, potentially were exposed to hydrazine sulfate (NIOSH 1990).

Regulations

Department of Transportation (DOT)

Hydrazine is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Hydrazine is listed as a hazardous air pollutant.

Prevention of Accidental Release: Threshold quantity (TQ) = 15,000 lb for hydrazine.

Urban Air Toxics Strategy: Hydrazine is identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb for hydrazine.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Reportable quantity (RQ) = 1 lb for hydrazine.

Threshold planning quantity (TPQ) = 1,000 lb for hydrazine.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of hydrazine = U133.

Hydrazine is listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

Hydrazine is not permitted in steam in food-treatment processes.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 1 ppm (1.3 mg/m³) for hydrazine.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.01 ppm for hydrazine.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 50 ppm for hydrazine.

Ceiling recommended exposure limit = 0.03 ppm (0.04 mg/m³) (2-h exposure) for hydrazine.

Hydrazine is listed as a potential occupational carcinogen.

References

- Akron. 2009. *The Chemical Database*. The Department of Chemistry at the University of Akron. <http://ull.chemistry.uakron.edu/erd> and search on CAS number for hydrazine and for hydrazine sulfate. Last accessed: 12/31/09.
- ATSDR. 1997. *Toxicological Profile for Hydrazine (Final Report)*. Agency for Toxic Substances and Disease Registry. <http://www.atsdr.cdc.gov/toxprofiles/tp100.pdf>.
- Boice JD Jr, Marano DE, Cohen SS, Mumma MT, Blot WJ, Brill AB, Fryzek JP, Henderson BE, McLaughlin JK. 2006. Mortality among Rocketdyne workers who tested rocket engines, 1948-1999. *J Occup Environ Med* 48(10): 1070-1092.
- ChemSources. 2009. Chemical Sources International. <http://www.chemsources.com/chemonline.html> and search on hydrazine and on hydrazine sulfate. Last accessed: 12/31/09.
- Doerr DF. 2001. Development of an advanced rocket propellant handler's suit. *Acta Astronautica* 49(3-10): 463-468.
- Durmugoglu E, Aslan S, Can E, Bulut Z. 2007. Health risk assessment of workers' exposure to organic compounds in a tire factory. *Hum Ecol Risk Assess* 13: 209-222.
- EPA. 2004. *Non-confidential IUR Production Volume Information*. U.S. Environmental Protection Agency. <http://www.epa.gov/oppt/iur/tools/data/2002-vol.html> and search on CAS number for hydrazine and for hydrazine sulfate. Last accessed: 12/31/09.
- EPA. 2009. *Non-confidential 2006 IUR Records by Chemical, Including Manufacturing, Processing and Use Information*. U.S. Environmental Protection Agency. http://cfpub.epa.gov/iursearch/2006_iur_companyinfo.cfm?chemid=4425.
- Helmert S, Ruland RT, Jacob LN. 2004. Epithelioid sarcoma of the thumb associated with hydrazine fuel exposure: a case report. *Mil Med* 169(1): 41-44.
- HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number for hydrazine and for hydrazine sulfate. Last accessed: 12/31/09.
- IARC. 1974. Hydrazine. In *Some Aromatic Amines, Hydrazine and Related Substances, N-Nitroso Compounds and Miscellaneous Alkylating Agents*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 4. Lyon, France: International Agency for Research on Cancer. pp. 127-136.
- IARC. 1987. Hydrazine. In *Overall Evaluations of Carcinogenicity*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, suppl. 7. Lyon, France: International Agency for Research on Cancer. pp. 223-224.
- IARC. 1999. Hydrazine. In *Re-evaluation of Some Organic Chemicals, Hydrazine, and Hydrogen Peroxide*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 71. Lyon, France: International Agency for Research on Cancer. pp. 991-1013.
- Korhonen K, Liukkonen T, Ahrens W, Astrakianakis G, Boffetta P, Burdorf A, *et al.* 2004. Occupational exposure to chemical agents in the paper industry. *Int Arch Occup Environ Health* 77(7): 451-460.
- Morris J, Densen JW, Wald NJ, Doll R. 1995. Occupational exposure to hydrazine and subsequent risk of cancer. *Occup Environ Med* 52(1): 43-45.
- NCI. 2008. *Hydrazine Sulfate (PDQ). Health Professional Version*. National Cancer Institute. Last updated: 5/20/08. <http://www.cancer.gov/cancertopics/pdq/cam/hydrazinesulfate/HealthProfessional>.

NIOSH. 1990. *National Occupational Exposure Survey (1981-83)*. National Institute for Occupational Safety and Health. Last updated: 7/1/90. <http://www.cdc.gov/noes/noes1/38110sic.html>, <http://www.cdc.gov/noes/noes1/x4065sic.html>.

PHS. 1982. *The Health Consequences of Smoking – Cancer: A Report of the Surgeon General*. U.S. Public Health Service. <http://profiles.nlm.nih.gov/NN/B/C/D/W>.

Ritz B, Morgenstern H, Froines J, Moncau J. 1999. Chemical exposures of rocket-engine test-stand personnel and cancer mortality in a cohort of aerospace workers. *J Occup Environ Med* 41(10): 903-910.

Ritz B, Zhao Y, Krishnadasan A, Kennedy N, Morgenstern H. 2006. Estimated effects of hydrazine exposure on cancer incidence and mortality in aerospace workers. *Epidemiology* 17(2): 154-161.

Roe FJ. 1978. Hydrazine. *Ann Occup Hyg* 21(3): 323-326.

Sax NI, Lewis RJ. 1987. *Hawley's Condensed Chemical Dictionary*. 11th ed., New York: Van Nostrand Reinhold. pp. 276, 490, 633, 635, 732.

SRI. 2009. *Directory of Chemical Producers*. Menlo Park, CA: SRI Consulting. Database edition. Last accessed: 12/30/09.

TRI. 2009. *TRI Explorer Chemical Report*. U.S. Environmental Protection Agency. <http://www.epa.gov/triexplorer> and select Hydrazine and select Hydrazine Sulfate. Last accessed: 12/31/09.

USITC. 2009. *USITC Interactive Tariff and Trade DataWeb*. United States International Trade Commission. http://dataweb.usitc.gov/scripts/user_set.asp and search on HTS no. 282510. Last accessed: 10/21/09.

Vernot EH, MacEwen JD, Bruner RH, Haun CC, Kinkead ER, Prentice DE, et al. 1985. Long-term inhalation toxicity of hydrazine. *Fundam Appl Toxicol* 5(6 Pt 1): 1050-1064.

Wald NJ. 1985. Hydrazine: epidemiological evidence. In *Interpretation of Negative Epidemiological Evidence in Carcinogenicity*. IARC Scientific Publications No. 65. Lyon, France: International Agency for Research on Cancer. pp. 75-80.

Wald N, Boreham J, Doll R, Bonsall J. 1984. Occupational exposure to hydrazine and subsequent risk of cancer. *Br J Ind Med* 41(1): 31-34.

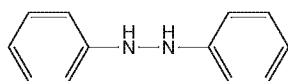
Hydrazobenzene

CAS No. 122-66-7

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as 1,2-diphenylhydrazine



Carcinogenicity

Hydrazobenzene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Dietary exposure to hydrazobenzene caused tumors in two rodent species and at several different tissue sites. It caused liver cancer (hepatocellular carcinoma) in female mice and male rats and benign liver tumors (hepatocellular adenoma) in female rats. In rats, it also caused mammary-gland cancer (adenocarcinoma) in females and increased the combined incidence of benign and malignant Zymbal-gland tumors (squamous-cell papilloma and carcinoma) in males (NCI 1978). Since hydrazobenzene was listed in the *Second Annual Report on Carcinogens*, an additional study in mice has been identified. Hydrazobenzene administered by intraperitoneal injection to strain A mice (a strain with a high spontaneous incidence of lung cancer) caused benign lung tumors (alveolar-bronchial adenoma) in males, but not in females (Maronpot et al. 1986).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to hydrazobenzene. A number of historical occupational cohort studies of workers in the benzidine-based-dye industry, who may be exposed to hydrazobenzene (a precursor of benzidine), found signifi-

cantly increased risks of bladder cancer (de Braud et al. 2002). Two case-control studies reported increased risks of bladder cancer among workers with potential exposure to chemical dyes, after controlling for smoking and other variables (Wynder et al. 1963, Anthony and Thomas 1970), prompting the National Cancer Institute to evaluate the carcinogenicity of hydrazobenzene in rodents (NCI 1978). In the studies of dye workers, hydrazobenzene exposure was not quantified and could not be distinguished from exposure to other chemicals, including benzidine, 2-naphthylamine, and 4-aminodiphenyl, which are known human carcinogens associated with bladder-cancer risk.

Properties

Hydrazobenzene is a hydrazine derivative that is a colorless crystal or tablet at room temperature. It is very soluble in ethanol, slightly soluble in benzene and deuterated dimethyl sulfoxide, insoluble in acetic acid, and practically insoluble in water (HSDB 2009). Hydrazobenzene is stable under normal temperatures and pressures (Akron 2009). Physical and chemical properties of hydrazobenzene are listed in the following table.

Property	Information
Molecular weight	184.2
Specific gravity	1.158 at 16°C/4°C
Melting point	131°C (decomposes)
Boiling point	293°C at 760 mm Hg
Log K_{ow}	2.94
Water solubility	221 mg/L at 25°C
Vapor pressure	0.00044 mm Hg at 25°C
Dissociation constant (pK_a)	-0.65

Source: HSDB 2009.

Use

Hydrazobenzene has been used primarily in the dye manufacturing industry as the precursor of the dye intermediate benzidine (HSDB 2009). It is also used as an intermediate in the manufacture of pharmaceuticals such as sulfinpyrazone and phenylbutazone, which have been used to treat gout (Roberts and Morrow 2001, HSDB 2009). Some minor direct uses of hydrazobenzene are in polymerization reactions and as an anti-sludging additive to motor oil, desuckering agent for tobacco plants, reductant in the reclamation of rubber, component of experimental organometallic polymers, and component in photochromic resin compositions (HSDB 2009). It is also used in the manufacture of hydrogen peroxide and has been evaluated for insecticidal activity.

Production

Production of at least 450,000 kg (992,000 lb) of hydrazobenzene was reported in 1977 (HSDB 2009). Dye-manufacturing facilities produced additional unknown quantities of hydrazobenzene as an intermediate in the production of benzidine, which is formed by the reduction of nitrobenzene to hydrazobenzene followed by the rearrangement of hydrazobenzene to benzidine (NCI 1978). Manufacturing of benzidine-based dyes ceased in 1988 (ATSDR 1990). In 2009, hydrazobenzene was produced by three manufacturers in India (SRI 2009) and was available from 26 suppliers worldwide, including 15 U.S. suppliers (ChemSources 2009). U.S. imports of hydrazobenzene were 72,100 kg (158,600 lb) in 1977 and 23,200 kg (51,000 lb) in 1982.

Exposure

The routes of potential human exposure to hydrazobenzene are inhalation, ingestion, and dermal contact. The potential for exposure to hydrazobenzene formerly was greatest in the benzidine-based-dye industry (NCI 1978, ATSDR 1990). The greatest potential for expo-

sure now is due to its use as an intermediate in the manufacture of certain pharmaceutical products. Because phenylbutazone and sulfinpyrazone can hydrolyze to hydrazobenzene, people who take these drugs to prevent gout attacks may be exposed to hydrazobenzene (ATSDR 1990). These drugs are used primarily in veterinary medicine; the extent of their current use in humans is unknown. In 2009, seven products approved by the U.S. Food and Drug Administration for use in humans contained sulfinpyrazone as an active ingredient, but all eleven pharmaceutical products containing phenylbutazone were listed as discontinued (FDA 2009).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, small quantities of hydrazobenzene have been released to air, surface water, and landfills. Annual releases of hydrazobenzene since 1998 have not exceeded 12 lb except in 2001, when 260 lb was released to an off-site nonhazardous-waste landfill. In 2007, one U.S. facility released 10 lb of hydrazobenzene to a hazardous-waste landfill (TRI 2009). Hydrazobenzene can exist in both particulate and vapor phases in the atmosphere. In the vapor phase, it degrades by reaction with photochemically produced hydroxyl radicals, with a half-life of 5 hours. In the particle phase, it can be removed by wet and dry deposition. If released to soil or water, it is expected to bind to soil, suspended solids, and sediment and have low soil mobility. It is not expected to volatilize readily from water or soil or to bioaccumulate to a large extent in aquatic organisms. Degradation of hydrazobenzene is reversible; hydrazobenzene undergoes oxidation to azobenzene under aerobic solutions, catalyzed by common environmental cations such as copper(II) and iron(III). In a municipal sewage effluent, the half-life for the decomposition of 100 µg of hydrazobenzene per liter was 60 minutes if oxygen was removed from the sewage, but only 15 minutes if the oxygen was not removed (ATSDR 1990). Hydrazobenzene was detected in 1.2% of 1,205 effluent samples collected from wastewater treatment plants in a national survey, at a median concentration of 10 µg/L (HSDB 2009). Hydrazobenzene was also found in drinking water at a concentration of 1 µg/L and was detected in fish taken from the Great Lakes.

The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 977 U.S. workers, including 154 women, potentially were exposed to hydrazobenzene (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Clean Water Act

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.036 µg/L; based on fish or shellfish consumption only = 0.20 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of hydrazobenzene = U109.

Listed as a hazardous constituent of waste.

References

- Akron. 2009. *The Chemical Database*. The Department of Chemistry at the University of Akron. <http://uakron.edu/chem/erd> and search on CAS number. Last accessed: 6/14/09.
- Anthony HM, Thomas GM. 1970. Tumors of the urinary bladder: An analysis of the occupations of 1,030 patients in Leeds, England. *J Natl Cancer Inst* 45(5): 879-895.
- ATSDR. 1990. *Toxicological Profile for 1,2-Diphenylhydrazine*. Agency for Toxic Substances and Disease Registry. <http://www.atsdr.cdc.gov/toxprofiles/tp136.pdf>.

ChemSources. 2009. *Chem Sources - Chemical Search*. Chemical Sources International. <http://www.chemsources.com/chemonline.html> and search on hydrazobenzene. Last accessed: 7/20/09.

De Braud F, Maffezzini M, Vitale V, Bruzzi P, Gatta G, Hendry WF, Sternberg CN. 2002. Bladder cancer. *Crit Rev Oncol Hematol* 41(1): 89-106.

FDA. 2009. *The Electronic Orange Book*. U.S. Food and Drug Administration. <http://www.fda.gov/cder/ob/default.htm> and select Search by Active Ingredient and search on hydrazobenzene. Last accessed: 7/20/09.

HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number. Last accessed: 7/20/09.

Maronpot RR, Shimkin MB, Witschi HP, Smith LH, Cline JM. 1986. Strain A mouse pulmonary tumor test results for chemicals previously tested in the National Cancer Institute carcinogenicity tests. *J Natl Cancer Inst* 76(6): 1101-1112.

NCI. 1978. *Bioassay of Hydrazobenzene for Possible Carcinogenicity*. Technical Report Series no. 92. DHEW (NIH) Publication No. 78-1342. Bethesda, MD: National Institutes of Health. 121 pp.

NIOSH. 1990. *National Occupational Exposure Survey (1981-83)*. National Institute for Occupational Safety and Health. Last updated: 7/1/90. <http://www.cdc.gov/noes/noes1/x5870sic.html>.

Pliss GB. 1974. [Carcinogenic properties of hydrazobenzene] [In Russian; English abstract]. *Vopr Onkol* 20(4): 53-57.

Roberts LJ II, Morrow JD. 2001. Analgesic-antipyretic and antiinflammatory agents and drugs employed in the treatment of gout. In *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 10th ed. Hardman JG, Limbird LE, Gilman A, eds. New York: McGraw-Hill. pp. 697-731.

SRI. 2009. *Directory of Chemical Producers*. Menlo Park, CA: SRI Consulting. Database edition. Last accessed: 7/20/09.

TRI. 2009. *TRI Explorer Chemical Report*. U.S. Environmental Protection Agency. <http://www.epa.gov/triexplorer> and select Hydrazobenzene. Last accessed: 7/20/09.

Wynder EL, Onderdonk J, Mantel N. 1963. An epidemiological investigation of cancer of the bladder. *Cancer* 16: 1388-1407.

Ionizing Radiation

Introduction

Ionizing radiation is electromagnetic radiation that has sufficient energy to remove electrons from atoms. Ionization results in the production of negatively charged free electrons and positively charged ionized atoms. Ionizing radiation can be classified into two categories: photons (X-radiation and gamma radiation) and particles (alpha and beta particles and neutrons). Five types or sources of ionizing radiation are listed in the Report on Carcinogens as *known to be human carcinogens*, in four separate listings:

- X-radiation and gamma radiation (included in one listing) were first listed in the *Eleventh Report on Carcinogens* (2004).
- Neutrons were first listed in the *Eleventh Report on Carcinogens* (2004).
- Radon and its isotopic forms radon-220 and radon-222, which emit primarily alpha particles, were first listed in the *Seventh Annual Report on Carcinogens* (1994).
- Thorium dioxide, which decays by emission of alpha particles, was first listed in the *Second Annual Report on Carcinogens* (1981).

Below are the profiles for the four ionizing radiation listings, covering carcinogenicity, properties, use, sources or production, exposure, and references cited separately for each profile, followed by a list of regulations and guidelines applicable to all five types or sources of ionizing radiation listed.

X-Radiation and Gamma Radiation

CAS No.: none assigned

Known to be human carcinogens

First listed in the *Eleventh Report on Carcinogens* (2004)

Also known as X-rays, gamma rays, and γ radiation

Carcinogenicity

X-radiation and gamma radiation are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Epidemiological studies of radiation exposure provide a consistent body of evidence for the carcinogenicity of X-radiation and gamma radiation in humans. Exposure to X-radiation and gamma radiation is most strongly associated with leukemia and cancer of the thyroid, breast, and lung; associations have been reported at absorbed doses of less than 0.2 Gy (see Properties, below, for explanation of radiation dose measurement). The risk of developing these cancers, however, depends to some extent on age at exposure. Childhood exposure is mainly responsible for increased leukemia and thyroid-cancer risks, and reproductive-age exposure for increased breast-cancer risk. In addition, some evidence suggests that lung-cancer risk may be most strongly related to exposure later in life. Associations between radiation exposure and cancer of the salivary glands, stomach, colon, urinary bladder, ovary, central nervous system, and skin also have been reported, usually at higher doses of radiation (1 Gy) (Kleinerman *et al.* 1995, Ron 1998, Ron *et al.* 1999, Brenner *et al.* 2000, Garwicz *et al.* 2000, Lichter *et al.* 2000, Sont *et al.* 2001, Yeh *et al.* 2001, Bhatia *et al.* 2002).

The first large study of sarcoma (using the U.S. Surveillance, Epidemiology, and End Results cancer registry) (Yap *et al.* 2002) added angiosarcoma to the list of radiation-induced cancers occurring within the field of radiation at high therapeutic doses. Two studies, one of workers at a Russian nuclear bomb and fuel reprocessing plant (Gilbert *et al.* 2000) and one of Japanese atomic-bomb survivors (Cologne *et al.* 1999), suggested that radiation exposure could cause liver cancer at doses above 100 mSv (in the worker population especially with concurrent exposure to radionuclides). Among the atomic-bomb survivors, the liver-cancer risk increased linearly with increasing radiation dose. A study of children medically exposed to radiation (other than for cancer treatment) provided some evidence that radiation exposure during childhood may increase the incidence of lymphoma and melanoma.

Studies on Mechanisms of Carcinogenesis

X-radiation and gamma radiation have been shown to cause a broad spectrum of genetic damage, including gene mutations, minisatellite mutations, micronucleus formation, chromosomal aberrations, ploidy changes, DNA strand breaks, and chromosomal instability. Genetic damage by X-radiation or gamma radiation has been observed in humans exposed accidentally, occupationally, or environmentally, in experimental animals exposed *in vivo*, and in cultured human and other mammalian cells. X-radiation and gamma radiation cause genetic damage in somatic cells and transmissible mutations in mammalian germ cells. The DNA molecule may be damaged directly, by interaction with ionizing radiation, or indirectly, by interaction with reactive products of the degradation of water by ionizing radiation (i.e., free electrons, hydrogen free radicals, or hydroxyl radicals) (IARC 2000, NTP 2003). The observed genetic damage is primarily the result of errors in DNA repair, but may also arise from errors in replication of damaged DNA. Epigenetic mechanisms that alter the action of genes also may be involved in radiation-induced carcinogenesis. Proposed mechanisms for delayed or indirect radiation-induced genetic damage include genomic instability, induction of mutations by irradiation of the cytoplasm of the cell, and “bystander effects,” in which genetic damage is induced in cells that were not directly exposed to ionizing radiation, apparently through cell signaling pathways.

Cancer Studies in Experimental Animals

X-radiation and gamma radiation are clearly carcinogenic in all species of experimental animals tested (mice, rats, and monkeys for X-radiation and mice, rats, rabbits, and dogs for gamma radiation). Among these species, radiation-induced tumors have been observed in at least 17 different tissue sites, including sites at which tumors were observed in humans (i.e., leukemia, thyroid gland, breast, and lung) (IARC 2000). Susceptibility to induction of tumors depends on tissue site, species, strain, age, and sex. Early prenatal exposure does not appear to cause cancer, but exposure at later stages of prenatal development has been reported to do so. It has been suggested that radiation exposure of mice before mating increases the susceptibility of their offspring to cancer; however, study results are conflicting.

Properties

As forms of electromagnetic radiation, X-rays and gamma rays are packets of energy (photons) having neither charge nor mass. They have essentially the same properties, but differ in origin. X-rays are emitted from processes outside the nucleus (e.g., bombardment of heavy atoms by fast-moving electrons), whereas gamma rays originate inside the nucleus (during the decay of radioactive atoms). The energy of ionizing radiation is expressed in electronvolts, a unit equal to the energy acquired by an electron when it passes through a potential difference of 1 volt in a vacuum; $1 \text{ eV} = 1.6 \times 10^{-19} \text{ J}$ (IARC 2000).

The energy of X-rays typically ranges from 5 to 100 keV. Lower in energy than gamma rays, X-rays are less penetrating; a few millimeters of lead can stop medical X-rays. The energy distribution of X-radiation is continuous, with a maximum at an energy about one third that of the most energetic electron. The energy of gamma rays resulting from radioactive decay typically ranges from 10 keV to 3 MeV. Gamma rays often accompany the emission of alpha or beta particles from a nucleus. Because of scattering and absorption within the radioactive source and the encapsulating material, the emitted photons have a relatively narrow energy spectrum (i.e., are monoenergetic). Gamma rays are very penetrating; they can easily pass through the human body, but they can also be absorbed by tissue. Several feet of concrete or a few inches of lead are required to stop the more energetic gamma rays (BEIR V 1990).

As photons interact with matter, their energy distribution is altered in a complex manner as a result of energy transfer. The amount of energy deposited by ionizing radiation per unit of path length in irradiated material is called the “linear energy transfer” (LET), expressed in units of energy per unit length (e.g., kiloelectronvolts per micrometer). X-rays and gamma rays are considered low-LET radiation. In tissue, they transfer their energy primarily to electrons. Compared with high-LET radiation (such as neutrons and alpha particles), low-LET radiation tends to follow more tortuous paths in matter, with more widely dispersed energy deposition.

Use

X-rays, gamma rays, and materials and processes that emit X-rays and gamma rays are used in medicine, the nuclear power industry, the military, scientific research, industry, and various consumer products.

Medical use of ionizing radiation in both diagnosis and therapy has been widespread since the discovery of X-rays by Wilhelm Conrad Roentgen in 1895, and radioactive sources have been used in radiotherapy since 1898. Advances in the latter half of the 20th century increased the use of medical radiation, and some newer techniques, particularly radiotherapy, computed tomography, positron emission tomography, and interventional radiation involving fluoroscopy, use higher radiation doses than do standard diagnostic X-rays. Radiation therapy may involve use of external beams of radiation, typi-

cally high-energy X-rays (4 to 50 MeV) and cobalt-60 gamma rays (UNSCEAR 2000).

Military uses of materials and processes that emit X-radiation and gamma radiation include the production of materials for nuclear weapons and the testing and use of nuclear weapons. In 1945, atomic bombs were detonated over Hiroshima and Nagasaki, Japan. Between 1945 and 1980, nuclear weapons were tested in the atmosphere of the Northern Hemisphere; during the most intense period of testing, from 1952 to 1962, about 520 tests were carried out (IARC 2000).

Several industrial processes use ionizing radiation. Industrial radiography uses gamma radiation to examine welded joints in structures. In the oil industry, gamma radiation or neutron sources are used to determine the geological structures in a bore hole (a process called “well logging”) (NCRP 1989). Ionizing radiation is also used to sterilize products and irradiate foods (to kill bacteria and parasites) (IARC 2000).

Ionization-type smoke detectors contain americium-241, which emits gamma radiation and alpha particles. In the past, detectors with up to 3.7 MBq of americium-241 were used in commercial and industrial facilities, but current smoke detectors contain less than 40 kBq (IARC 2000). Television sets emit low-energy X-rays through a process by which electrons are accelerated and bombard the screen (ATSDR 1999). Other products containing sources of ionizing radiation (of unspecified types) include radioluminescent clocks and watches, gaseous tritium light devices (e.g., self-luminous signs), thoriated gas lamp and lantern mantles, radioactive attachments to lightning conductors, static elimination devices, fluorescent lamp starters, porcelain teeth, gemstones activated by neutrons, and thoriated tungsten welding rods. For all of these products, the maximum allowable radioactivity is restricted, and radiation from these products contributes little to overall exposure of the population (IARC 2000).

Sources

The most important sources of X-radiation and gamma radiation include natural sources, medical uses, atmospheric nuclear weapons tests, nuclear accidents, and nuclear power generation. Ionizing radiation is present naturally in the environment from cosmic and terrestrial sources. Cosmic radiation is a minor source of exposure to X-radiation and gamma radiation; most natural exposure is from terrestrial sources. Soil contains radioactivity derived from the rock from which it originated. However, the majority of radioactive elements are chemically bound in the earth's crust and are not a source of radiation exposure unless released through natural forces (e.g., earthquake or volcanic activity) or human activities (e.g., mining or construction). Generally, only the upper 25 cm of the earth's crust is considered a significant source of gamma radiation. Indoor sources of gamma radiation may be more important than outdoor sources if earth materials (stone, masonry) were used in construction (IARC 2000).

Exposure

Biological damage by ionizing radiation is related to dose and dose rate, which may affect the probability that cancer will occur (IARC 2000). Radiation dose is a measure of the amount of energy deposited per unit mass of tissue and may be expressed as the absorbed dose, equivalent dose, or effective dose. The standard unit for absorbed dose is the gray, which is equal to 1 J/kg of deposited energy. The absorbed dose formerly was expressed in rads (1 Gy = 100 rads). The biological effect of high-LET radiation is greater than that of low-LET radiation at the same absorbed dose; therefore, a dose measurement independent of radiation type was derived to reflect the biological effectiveness of radiation in causing tissue damage. The “equivalent

dose” (also known as the “dose equivalent”) is obtained by multiplying the absorbed dose by a radiation weighting factor (W_R ; formerly called the “quality factor”). Radiation weighting factors are assigned to radiation of different types and energies by the International Commission on Radiological Protection based on their biological effects relative to those of a reference radiation, typically X-rays or gamma rays; W_R ranges from 1 (for low-LET radiation) to 20 (for high-LET radiation). The standard unit for the equivalent dose is the sievert. The equivalent dose formerly was expressed in rems (1 Sv = 100 rem). Because $W_R = 1$ for both X-rays and gamma rays, the absorbed and equivalent doses are the same (ICRP 1991). Another measurement, the “effective dose,” takes into account the fact that the same equivalent dose of radiation causes more significant biological damage to some organs and tissues than to others. Tissue weighting factors (W_T) are assigned to the various organs and tissue types, and the effective dose is calculated as the sum of the tissue-weighted equivalent doses in all exposed tissues and organs in an individual. The effective dose is expressed in sieverts. The collective radiation dose received by a given population may be expressed as the “collective equivalent dose” (also known as the “collective dose equivalent”), which is the sum of the equivalent doses received by all members of the population, or as the “collective effective dose,” which is the sum of the effective doses received by all members of the population. Both the collective equivalent dose and the collective effective dose are expressed in person-sieverts.

All individuals are exposed to ionizing radiation from a variety of natural and anthropogenic sources. Of the general population's exposure to all types of ionizing radiation (not just X-radiation and gamma radiation), natural sources contribute over 80%; radon gas and its decay products account for about two thirds of natural exposure, and the other third is from cosmic radiation, terrestrial radiation, and internally deposited radionuclides. The remaining exposure to ionizing radiation is from anthropogenic sources, such as medical procedures (15%), consumer products (3%), and other sources (totaling less than 1%), which include occupational exposure, nuclear fallout, and the nuclear fuel cycle (BEIR V 1990). In 2000, the worldwide estimated average annual per-capita effective doses of ionizing radiation (of any type) were 2.4 mSv (range = 1 to 20 mSv) for natural background exposure and 0.4 mSv (range = 0.04 to 1 mSv) for medical diagnostic exposure. However, in countries with the highest level of health care (< 1,000 population per physician), the average radiation dose from medical X-rays was estimated at 1.2 mSv, or about half the average natural exposure level. Estimated average annual effective doses from past atmospheric nuclear testing, the nuclear power plant accident in Chernobyl, Ukraine, and nuclear power production were only 0.005 mSv, 0.002 mSv, and 0.0002 mSv, respectively (UNSCEAR 2000).

Radiation exposure from medical uses is much more variable than that from natural background radiation (even though the latter varies considerably among locations) because of marked differences in the quality of medical care among cultures. In the more developed nations, higher percentages of the population receive regular medical care, and thus exposures from diagnostic radiology and radiotherapy tend to be higher than in developing nations. Exposure to diagnostic X-rays varies but generally is low; plain film examinations of the chest and extremities involve relatively low effective doses (0.05 to 0.4 mSv), whereas examinations of the abdomen and lumbar spine or pelvis may result in higher effective doses (1 to 3 mSv). Radiation therapy uses much larger doses of radiation than do diagnostic procedures. For example, treatment for leukemia usually involves irradiation of the total bone marrow, with absorbed doses of about 10 to 20 Gy delivered in several fractions (UNSCEAR 2000).

Excluding uranium miners and other workers whose radiation exposure is individually monitored, about 5 million people worldwide are occupationally exposed to natural sources of ionizing radiation (of any type) at levels above the natural background. About 75% are coal miners (whose estimated average annual effective dose is 1 to 2 mSv), about 13% are other underground miners (whose estimated average annual dose is 1 to 10 mSv), and about 5% are airline crews (who receive an estimated average annual dose of up to 3 mSv). Miners are exposed mainly through inhalation of radon; thus, they are exposed primarily to alpha particles, but also to gamma radiation. Airline crews are exposed primarily to gamma radiation, but also to neutrons (UNSCEAR 1993, IARC 2000).

Medical workers may be exposed to many different types of radionuclides and radiation. In the early 20th century, before radiation hazards were recognized, radiologists were exposed to high doses of X-radiation (IARC 2000). The first dose limit established for radiologists, in 1902, allowed exposure of approximately 30 Gy per year (Mabuchi 2002), but doses are now much lower (< 1 mSv) (Mostafa *et al.* 2002). Other settings with potential for occupational exposure to X-radiation or gamma radiation include the nuclear industry, military activities, research laboratories, and various industries where radioactive materials or radiography are used (IARC 2000).

References

- ATSDR. 1999. *Toxicological Profile for Ionizing Radiation*. Agency for Toxic Substances and Disease Registry. <http://www.atsdr.cdc.gov/ToxProfiles/tp149.pdf>.
- BEIR V. 1990. *Health Effects of Exposure to Low Levels of Ionizing Radiation*. Biological Effects of Ionizing Radiation Series. Washington, DC: National Academy Press. 421 pp.
- Bhatia S, Sather HN, Pabustan OB, Trigg ME, Gaynon PS, Robison LL. 2002. Low incidence of second neoplasms among children diagnosed with acute lymphoblastic leukemia after 1983. *Blood* 99(12): 4257-4264.
- Brenner DJ, Curtis RE, Hall EJ, Ron E. 2000. Second malignancies in prostate carcinoma patients after radiotherapy compared with surgery. *Cancer* 88(2): 398-406.
- Cologne JB, Tokuoka S, Beebe GW, Fukuhara T, Mabuchi K. 1999. Effects of radiation on incidence of primary liver cancer among atomic bomb survivors. *Radiat Res* 152(4): 364-373.
- Garwicz S, Anderson H, Olsen JH, Dollner H, Hertz H, Jonmundsson G, *et al.* 2000. Second malignant neoplasms after cancer in childhood and adolescence: a population-based case-control study in the 5 Nordic countries. *Int J Cancer* 88(4): 672-678.
- Gilbert ES, Koshurnikova NA, Sokolnikov M, Khokhryakov VF, Miller S, Preston DL, *et al.* 2000. Liver cancers in Mayak workers. *Radiat Res* 154(3): 246-252.
- IARC. 2000. X-Radiation and γ radiation. In *Ionizing Radiation, Part 1: X- and Gamma Radiation, and Neutrons*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 75. Lyon, France: International Agency for Research on Cancer. pp. 121-359.
- ICRP. 1991. *Recommendations of the International Commission on Radiological Protection*. International Commission of Radiological Protection Publication 60. Oxford: Pergamon Press. pp. 5-9.
- Kleinerman RA, Boice JD Jr, Storm HH, Sørensen P, Andersen A, Pukkala E, Lynch CF, Hankey BF, Flannery JT. 1995. Second primary cancer after treatment for cervical cancer. An international cancer registries study. *Cancer* 76(3): 442-452.
- Lichter MD, Karagas MR, Mott LA, Spencer SK, Stukel TA, Greenberg ER. 2000. Therapeutic ionizing radiation and the incidence of basal cell carcinoma and squamous cell carcinoma. *Arch Dermatol* 136(8): 1007-1011.
- Mabuchi K, Yoshinaga S, Ron E. 2002. Medical radiation exposures in occupational studies: overview of occupational medical exposure. *Radiat Res* 158(6): 803-804.
- Mostafa G, Sing RF, McKeown R, Huynh TT, Heniford BT. 2002. The hazard of scattered radiation in a trauma intensive care unit. *Crit Care Med* 30(3): 574-576.
- NCRP. 1989. *Exposure of the U.S. Population from Occupational Radiation*. NCRP Report No. 101. Bethesda, MD: National Council on Radiation Protection and Measurements. 75 pp.
- NTP. 2003. *Report on Carcinogens Background Document for X-Radiation & Gamma Radiation and Neutrons*. National Toxicology Program. http://ntp.niehs.nih.gov/ntp/newhomero/roc11/IR_RG2_Public.pdf.
- Ron E. 1998. Ionizing radiation and cancer risk: evidence from epidemiology. *Radiat Res* 150(5 Suppl): S30-S41.
- Ron E, Auvainen A, Alfandary E, Stovall M, Modan B, Werner A. 1999. Cancer risk following radiotherapy for infertility or menstrual disorders. *Int J Cancer* 82(6): 795-798.
- Sont WN, Zielinski JM, Ashmore JP, Jiang H, Krewski D, Fair ME, Band PR, Letourneau EG. 2001. First analysis of cancer incidence and occupational radiation exposure based on the National Dose Registry of Canada. *Am J Epidemiol* 153(4): 309-318.
- UNSCEAR. 1993. *Sources and Effects of Ionizing Radiation. 1993 Report to the General Assembly*. New York: United Nations Scientific Committee on the Effects of Atomic Radiation.

UNSCEAR. 2000. *Sources and Effects of Ionizing Radiation. 2000 Report to the General Assembly with Scientific Annexes*. New York: United Nations Scientific Committee on the Effects of Atomic Radiation.

Yap J, Chuba PJ, Thomas R, Aref A, Lucas D, Severson RK, Hamre M. 2002. Sarcoma as a second malignancy after treatment for breast cancer. *Int J Radiat Oncol Biol Phys* 52(5): 1231-1237.

Yeh H, Matanoski GM, Wang N, Sandler DP, Comstock GW. 2001. Cancer incidence after childhood nasopharyngeal radium irradiation: a follow-up study in Washington County, Maryland. *Am J Epidemiol* 153(8): 749-756.

Neutrons

CAS No.: none assigned

Known to be a human carcinogen

First listed in the *Eleventh Report on Carcinogens* (2004)

Carcinogenicity

Neutrons are *known to be a human carcinogen* based on studies on their mechanisms of carcinogenesis, which demonstrated that neutrons cause genetic damage in humans similar to that caused by X-radiation and gamma radiation, induce chromosomal aberrations in humans, and produce gamma radiation when they interact with biological materials. In addition, there is sufficient evidence of carcinogenicity from studies in experimental animals.

Studies on Mechanisms of Carcinogenesis

Neutrons cause a broad spectrum of genetic damage similar to that caused by X-radiation and gamma radiation, including gene mutations, micronucleus formation, sister chromatid exchange, chromosomal aberrations, DNA strand breaks, and chromosomal instability. Genetic damage by neutron radiation has been observed in humans exposed occupationally or medically, in experimental animals exposed *in vivo*, and in cultured human and other mammalian cells. Studies of humans exposed to neutron radiation showed that induced chromosomal aberrations persisted for decades, and some cell-culture studies showed genomic instability in the progeny of irradiated human cells (IARC 2000, Littlefield *et al.* 2000). Many cell-culture studies have consistently demonstrated that neutron radiation causes chromosomal aberrations in human peripheral-blood lymphocytes more effectively than does gamma radiation (IARC 2000). Reciprocal translocations in male germ cells were observed in rhesus monkeys.

Although the genetic damage caused by neutron radiation is qualitatively similar to that caused by X-radiation and gamma radiation, it differs quantitatively. Low-energy neutrons, such as fission neutrons (those resulting from the splitting of atomic nuclei), are significantly more potent carcinogens in experimental animals than is low-LET radiation, such as X-rays or gamma rays. Types of ionizing radiation with differing LET differ in their effects on biological tissue; however, the observed differences are not sufficient to indicate that the biological effects of high-LET (i.e., neutrons) and low-LET radiation differ qualitatively. In general, neutron radiation induces chromosomal aberrations, mutations, and DNA damage more efficiently than does low-LET radiation. DNA lesions caused by neutron radiation are more severe and are repaired less efficiently, and neutron radiation induces higher proportions of complex chromosomal aberrations (Pogozelski *et al.* 1999, Boei *et al.* 2001, Brenner *et al.* 2001). However, there is no conclusive evidence of a signature alteration that might distinguish tumors induced by high-LET radiation from those induced by low-LET radiation.

Cancer Studies in Experimental Animals

Neutrons are clearly carcinogenic in all species of experimental animals tested, including mice, rats, rabbits, dogs, and monkeys. Among

these species, radiation-induced tumors have been observed in at least 20 different tissue sites, including sites at which tumors were observed in humans (i.e., leukemia, thyroid gland, breast, and lung) (IARC 2000). Susceptibility to induction of tumors depends on tissue site, species, strain, age, and sex.

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to neutron radiation.

Properties

Neutrons are electrically neutral particles found in the nuclei of atoms and are similar in mass to protons, which also are present in the nucleus. Because neutrons have no electrical charge, they do not interact with atomic electrons, but they do interact with atomic nuclei. The nuclear force, which holds particles together in the nucleus and leads to these interactions, has a very short range, which means that a neutron must pass close to a nucleus for an interaction to take place. These atomic interactions generate protons, alpha particles, and other nuclear fragments, along with gamma radiation. Because of the small size of the nucleus in relation to the atom as a whole, neutrons have a low probability of interaction and thus are very penetrating. Depending on their energy, they can travel up to several tens of centimeters through tissue (IARC 2000). Water (in nuclear reactors) and thick concrete (in particle accelerators) typically are used as shielding, because interactions with hydrogen nuclei (single protons, which are similar in mass to neutrons) are most effective at reducing neutron energy.

Neutrons cause ionization in biological tissue through elastic collisions with the nuclei of atoms composing tissue molecules. In collisions of neutrons with the hydrogen nuclei of water (the major component of the human body), the recoiling hydrogen nuclei (charged protons) are the source of ionizing events. Elastic collisions of high-energy neutrons (over 50 MeV) with larger nuclei, such as those of carbon, oxygen, nitrogen, and calcium atoms, result in violent interactions that produce many low-energy charged particles. Because the masses of protons and the other recoiling nuclei are much greater than the mass of an electron, neutron radiation generates a dense ion path, causing more damage to tissue than a similar dose of X-rays or gamma rays. Neutrons therefore are considered high-LET radiation. With each collision, about half of the neutron's energy is given to the proton. As the neutron loses energy, it slows down until it is absorbed into the nucleus of an atom, which often makes the absorbing atom radioactive (IARC 2000, Busby 2001).

Use

Neutron radiation is used less than other types of radiation in industry, medicine, and research. Neutron radiation has not been used widely for medical purposes, because it has not shown clear therapeutic benefits, compared with conventional radiotherapy. However, there has been renewed interest in fast-neutron therapy for some cancers (Britten *et al.* 2001, Forman *et al.* 2002). Current medical uses of neutrons include external beam therapy, boron neutron capture therapy, and production of radioisotopes used in medical diagnosis and cancer therapy. Neutron sources are used in oil-well logging and to induce chain reactions in nuclear reactors. Other uses include neutron activation analysis and radiography (for determination of the elemental composition and moisture content of various materials), sterilization of materials, radiometric dating of rocks, and scientific and engineering research (ATSDR 1999, IARC 2000, Lowy *et al.* 2001).

Sources

The atomic nucleus is the source of all neutron radiation, but neutrons can be released in several ways. Because the nuclear constituents are tightly bound, several million electronvolts are required to free a neutron from most nuclei (IARC 2000). Sources of neutron radiation include the following: the interaction of high-energy cosmic rays with the earth's atmosphere, nuclear fusion or fission of atomic nuclei in nuclear reactors or atomic explosions, collision of charged particles with a lithium or beryllium target, and spontaneous fission of californium-252 (ATSDR 1999, IARC 2000).

Exposure

The worldwide population is exposed to neutron radiation from natural sources. Populations with additional exposure include cancer patients receiving radiation therapy, nuclear-industry workers, survivors of atomic bomb blasts, and airline crews and passengers. In almost all cases, individuals are exposed to mixed radiation fields in which neutrons are a minor component. Exceptions are patients receiving neutron radiotherapy and airline crews and passengers, who may receive up to 60% of their equivalent dose from neutron radiation.

The general population is exposed to neutrons primarily from cosmic radiation originating from outer space; however, only the most energetic particles produce effects at ground level (IARC 2000). A small portion of cosmic radiation originates from the sun. The amount increases during periods of increased sunspot and solar-flare activity, which run in approximately 11-year cycles; the largest event to date occurred in February 1956, when neutron counts at ground level rose 3,600% above normal background levels (ATSDR 1999, IARC 2000). The average dose of neutron radiation from cosmic radiation increases at higher altitudes; the dose in Denver, Colorado, at an altitude of 1,600 m (1 mi) is about twice that received at sea level (IARC 2000). The estimated annual effective dose of neutron radiation at sea level at 50° latitude is 80 μ Sv (UNSCEAR 2000). The atomic bombs exploded over Hiroshima and Nagasaki, Japan, in 1945 released low levels of neutron radiation to the environment (an estimated 1% to 2% of the total dose of ionizing radiation from the bombs was from neutrons) (IARC 2000).

Airline crews and passengers are exposed to varying doses of neutron radiation, depending on flight route, aircraft type, and number of hours in flight. Annual average equivalent doses for airline crews have been estimated to range from 0.6 to 3.6 mSv. Collective equivalent doses of neutron radiation received by passengers have been estimated based on air travel rates. For example, in 1985, total time in flight was estimated as 3×10^9 passenger hours; based on an estimated average equivalent dose rate of 1.6 μ Sv per hour, the annual collective equivalent dose was 5,040 person-Sv. By 1997, time in flight had grown to 4.3×10^9 passenger hours, resulting in an annual collective equivalent dose of 7,200 person-Sv (IARC 2000).

Occupational exposure to neutron radiation occurs to a limited extent in the nuclear industry; however, these workers are exposed primarily to gamma radiation. A study using data from 1977 to 1984 estimated the average annual effective dose of neutron radiation among U.S. radiation workers employed by Department of Energy contractors, nuclear power stations, and the U.S. Navy to be 1.8 mSv and the collective effective dose to be 67.5 person-Sv (IARC 2000). In another U.S. study, the average equivalent dose of neutron radiation to nuclear power plant workers was 5.6 mSv, and the collective equivalent dose was 0.038 person-Sv (NCRP 1989). Overall, less than 3% of the total annual effective radiation dose to nuclear industry workers in the United Kingdom from 1946 to 1988 was due to neutrons (Carpenter *et al.* 1994). Workers involved in the production of nuclear weapons may be exposed to low levels of neutron radiation. In

1979, 24,787 U.S. workers in DOE facilities (80% of whom performed defense-related work) were monitored for exposure to neutron radiation; only 326 (1.4%) received annual equivalent doses higher than 5 mSv (IARC 2000). Oil-field workers may be exposed to low doses of neutron radiation during well logging; the average annual equivalent dose was estimated at 1 to 2 mSv (Fujimoto *et al.* 1985).

References

ATSDR. 1999. *Toxicological Profile for Ionizing Radiation*. Agency for Toxic Substances and Disease Registry. <http://www.atsdr.cdc.gov/ToxProfiles/tp149.pdf>.

Boei JJ, Vermeulen S, Mullenders LH, Natarajan AT. 2001. Impact of radiation quality on the spectrum of induced chromosome exchange aberrations. *Int J Radiat Biol* 77(8): 847-857.

Brenner DJ, Okladnikova N, Hande P, Burak L, Geard CR, Azizova T. 2001. Biomarkers specific to densely-ionising (high LET) radiations. *Radiat Prot Dosimetry* 97(1): 69-73.

Britten RA, Peters LJ, Murray D. 2001. Biological factors influencing the RBE of neutrons: implications for their past, present and future use in radiotherapy. *Radiat Res* 156(2): 125-135.

Busby B. 2001. *Answer to Question #609 Submitted to "Ask the Experts." Category: Radiation Basics - Neutrons*. Health Physics Society. Last updated: 12/31/03. <http://hps.org/publicinformation/ate/q609.html>.

Carpenter L, Higgins C, Douglas A, Fraser P, Beral V, Smith P. 1994. Combined analysis of mortality in three United Kingdom nuclear industry workforces, 1946-1988. *Radiat Res* 138(2): 224-238.

Forman JD, Yudelev M, Bolton S, Tekyi-Mensah S, Maughan R. 2002. Fast neutron irradiation for prostate cancer. *Cancer Metastasis Rev* 21(2): 131-135.

Fujimoto K, Wilson JA, Ashmore JP. 1985. Radiation exposure risks to nuclear well loggers. *Health Phys* 48(4): 437-445.

IARC. 2000. Neutrons. In *Ionizing Radiation, Part 1: X- and Gamma Radiation, and Neutrons*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 75. Lyon, France: International Agency for Research on Cancer. pp. 363-448.

Littlefield LG, McFee AF, Sayer AM, O'Neill JP, Kleinerman RA, Maor MH. 2000. Induction and persistence of chromosome aberrations in human lymphocytes exposed to neutrons *in vitro* or *in vivo*: Implications of findings in "retrospective" biological dosimetry. *Radiat Prot Dosim* 88(1): 59-68.

Lowy RJ, Vavrina GA, LaBarre DD. 2001. Comparison of gamma and neutron radiation inactivation of influenza A virus. *Antiviral Res* 52(3): 261-273.

NCRP. 1989. *Exposure of the U.S. Population from Occupational Radiation*. NCRP Report No. 101. Bethesda, MD: National Council on Radiation Protection and Measurements. 75 pp.

Pogozelski WK, Xapsos MA, Blakely WF. 1999. Quantitative assessment of the contribution of clustered damage to DNA double-strand breaks induced by ⁶⁰Co gamma rays and fission neutrons. *Radiat Res* 151(4): 442-448.

UNSCEAR. 2000. *Sources and Effects of Ionizing Radiation. 2000 Report to the General Assembly with Scientific Annexes*. New York: United Nations Scientific Committee on the Effects of Atomic Radiation.

Radon

CAS No. 10043-92-2

Known to be a human carcinogen
First listed in the *Seventh Annual Report on Carcinogens* (1994)
Also known as Rn

Carcinogenicity

Radon and its isotopic forms radon-222 and radon-220 are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Increased incidences of lung cancer have been reported in numerous epidemiological studies of groups occupationally exposed to radon at high doses (IARC 1988, ATSDR 1990). Evidence supporting this listing was based principally on earlier mortality studies of underground mine workers. In one of the largest prospective studies, two cohorts totaling 3,400 white and 780 Native American uranium miners and millers in Colorado were followed from 1950 to 1977. Among white males, the risk of lung cancer was significantly increased 4- to 6-fold, depending on the comparison population used; the risk of cancer at other tissue sites was not increased. The risk of lung cancer increased significantly with increasing cumulative radon exposure, supporting

a causal relationship. Other prospective and retrospective cohort and case-control studies of uranium miners, together with studies of miners of iron ore (hematite), other metals, and fluorite, conducted between the 1960s and 1980s consistently found that lung-cancer risk increased with increasing cumulative exposure (despite some methodological limitations in exposure estimation, particularly in retrospective studies). In some cohorts, radon exposure was also associated with increased risks of tracheal and bronchial cancer. Smaller case-control studies also suggested an association between lung-cancer risk and indoor residential exposure to radon, mainly from ground sources (IARC 1988).

Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of radon from studies in experimental animals. In male rats, inhalation exposure to radon caused lung cancer (adenoma, adenocarcinoma, alveolar/bronchiolar carcinoma, and squamous-cell carcinoma), and incidences of respiratory-tract tumors were increased further by exposure to both radon and cigarette smoke or cerium hydroxide particles. In dogs of both sexes, inhalation exposure to a combination of radon, radon decay products, and uranium ore dust caused lung cancer (epidermoid carcinoma, alveolar/bronchiolar carcinoma, and fibrosarcoma) and nasal cancer (carcinoma). A review of studies in rats exposed to radon by inhalation also reported increased incidences of tumors of the upper lip and urinary tract. In a study in hamsters, only three animals developed features of squamous-cell carcinoma after 16 to 17 months of exposure to radon decay products or radon decay products and uranium ore dust. The International Agency for Research on Cancer (IARC 1988, 2001) concluded that there was sufficient evidence for the carcinogenicity of radon and its decay products in experimental animals.

Properties

Radon is a naturally occurring element and is the heaviest of the noble (chemically inert) gases. Of radon's 20 known isotopes, only three occur naturally, all of which are radioactive. Radon-222, produced by the decay of radium-226, is the most common and most stable isotope, with a half-life of 3.82 days. Radon-220, or thoron, is produced in the decay series of thorium-232 and has a half-life of 55 seconds. Radon-219, or actinon, is produced in the decay series of uranium-235 and has a half-life of 4 seconds (CEE 2003). Radon is colorless, tasteless, and odorless and is fairly soluble in water and organic solvents. It spontaneously decays into a series of short-lived radioisotopes of heavy metals (polonium, lead, and bismuth) commonly referred to as "radon daughters" or "radon progeny." Decay of radon and of its decay products results in the release of alpha particles and gamma radiation. When radon is released into air, its solid decay products readily attach to airborne dust (IARC 1988, ATSDR 1990). Physical and chemical properties of radon are listed in the following table.

Property	Information
Density	9.73 g/L at 0°C
Melting point	-71°C
Boiling point	-61.8°C
Vapor pressure	395.2 mm Hg at -71°C

Source: ATSDR 1990.

Use

Radon is used primarily for research; it has no significant industrial uses. It is used to initiate and influence chemical reactions, as a surface label in the study of surface reactions, in combination with beryllium or other light materials as a source of neutrons, in petroleum and uranium exploration, and in earthquake prediction (ATSDR 1990,

HSDB 2009). In U.S. locations with naturally high levels of radon in water or air, exposure to radon has been used since the early 1900s to purportedly treat a wide variety of diseases, such as skin disorders, hardening of the arteries, ulcers, allergies, arthritis, and high blood pressure. Radon also was used to treat malignant tumors; it was encapsulated in gold “seeds,” which were implanted at the tumor site (ATSDR 1990).

Production

Radon is produced in nature by radioactive decay of radium. Radon-222 is produced by decay of radium-226, a long-lived product of the uranium-238 decay series. Radon-220 is produced by decay of radium-224 in the thorium-232 decay series, and radon-219 by decay of radium-223 in the uranium-235 decay series. It is estimated that every square mile of soil to a depth of 6 inches contains about 1 g of radon. Radon is released from soil into air and groundwater, and thus occurs at low concentrations throughout the environment. Radon concentrations are highest in areas with uranium and thorium ore deposits and granite formations (ATSDR 1990). Radon-222 makes by far the largest contribution to environmental radon concentrations and is the isotope on which exposure estimates have been based (IARC 2001).

Radon was produced commercially for use in radiation therapy, but for the most part has been replaced by other radionuclides. Some radon is produced in research laboratories and universities for use in experimental studies. Radon is not imported or exported by the United States (ATSDR 1990, HSDB 2009).

Exposure

Among the general population, radon accounts for about half of the worldwide average annual background effective dose of radiation, which is 2.4 mSv (IARC 2001). Elevated radon levels have been discovered at locations in virtually every U.S. state, but levels vary considerably, even within a given location. The U.S. Environmental Protection Agency developed a generalized map of U.S. radon zones by county, based on predicted average indoor radon screening levels: Zone 1 includes counties with predicted levels above 4 pCi/L (148 Bq/m³), Zone 2 includes counties with predicted levels between 2 and 4 pCi/L, and Zone 3 includes counties with predicted levels below 2 pCi/L (74 Bq/m³) (EPA 2003a). In general, Zone 1 areas are concentrated in the northern half of the United States and the Appalachian mountains, and Zone 3 areas are concentrated in the piedmont and coast of the Southeast, Louisiana, Arkansas, Oklahoma, and Texas, and on the Northwest coast. EPA estimates that 1 in 15 homes have elevated radon levels (4 pCi/L or higher). As of 2003, radon exposure in U.S. single-family homes was thought to be a causal factor in as many as 15,000 to 22,000 lung cancer deaths per year (EPA 2003b).

The primary routes of environmental exposure to radon are inhalation and ingestion. Radon in groundwater, soil, or building materials enters working and living spaces and decays, emitting ionizing radiation. Environmental radon concentrations vary with geographical location and other factors. Average radon concentrations in U.S. groundwater are about 8.8 Bq/L in large aquifers and 28.9 Bq/L in small aquifers and wells. In the continental United States, concentrations in outdoor air range from about 4.1 to 15.2 Bq/m³, with a mean of about 8.9 Bq/m³. However, concentrations of up to 30 Bq/m³ were measured on the Colorado Plateau. Average radon levels are higher in indoor than outdoor air; indoor levels reportedly range from 55 to 157 Bq/m³ (ATSDR 1990). Emanation of radon from rock, soil, and groundwater can cause significant radon concentrations in tunnels, power stations, caves, public baths, and spas (IARC 1988).

Workers employed in uranium, hard-rock, and phosphate mining potentially are exposed to radon at high concentrations. Uranium miners generally are believed to have the highest exposures. However, the number of operating U.S. underground uranium mines decreased from 300 in 1980 to only 16 in 1984, and the number of underground uranium mine workers from 9,000 in 1979 to 448 in 1986. Concentrations of radon decay products in the air of underground mines vary. Annual geometric mean concentrations of radon decay products in U.S. uranium mines from 1976 to 1985 ranged from 800 to 2,664 Bq/m³, while concentrations in phosphate mines ranged from 888 to 8,880 Bq/m³. Radon exposure in underground mines has been greatly reduced through engineering controls. In New Mexico mines, implementation of control measures reduced radon exposure by an order of magnitude from 1967 to 1980 (ATSDR 1990).

References

- ATSDR. 1990. *Toxicological Profile for Radon*. ATSDR/TP-90/23. Atlanta, GA: Agency for Toxic Substances and Disease Registry. 170 pp.
- CEE. 2003. *Radon, Compounds and Elements*. Columbia Electronic Encyclopedia. <http://1upinfo.com/encyclopedia/R/radon.html>. Last accessed: 1/12/04.
- EPA. 2003a. *Map of Radon Zones*. U.S. Environmental Protection Agency. Last updated: 7/1/03. <http://www.epa.gov/radon/zonemap.html>.
- EPA. 2003b. *Home Buyer's and Seller's Guide to Radon*. U.S. Environmental Protection Agency. Last updated: 3/24/03. <http://www.epa.gov/radon/pubs/hmbyguid.html>.
- HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number. Last accessed: 10/22/09.
- IARC. 1988. Radon. In *Man-made Fibers and Radon*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 43. Lyon, France: International Agency for Research on Cancer. pp. 173-259.
- IARC. 2001. Radon. In *Some Internally Deposited Radionuclides*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 78. Lyon, France: International Agency for Research on Cancer. pp. 137-167.

Thorium Dioxide

CAS No. 1314-20-1

Known to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as thorium oxide



Carcinogenicity

Thorium dioxide is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Evidence for the carcinogenicity of thorium dioxide comes from follow-up epidemiological studies of patients who received intravascular injections of Thorotrast (thorium dioxide used as a contrast agent in medical radiology; see Use, below). A large excess of liver tumors (primarily cholangiocellular tumors and hemangiosarcoma) was observed in the Thorotrast-treated patients. Excesses of other cancer, including leukemia and bone cancer, were reported in other studies (van Kaick *et al.* 1978, da Motta *et al.* 1979, Faber 1979, Mori *et al.* 1979).

Since thorium dioxide was listed in the *Second Annual Report on Carcinogens*, additional follow-ups of the Thorotrast cohorts have been reported. These cohort studies were reviewed by the International Agency for Research on Cancer in its evaluation of *Some Internally Deposited Radionuclides* (IARC 2001). IARC reported the results of five major cohort studies (in Germany, Denmark, Japan, Portugal, and Sweden), which followed over 10,000 patients injected with Thorotrast between the 1930s and 1950s. These studies con-

firmed the findings of the earlier studies and reported relative risks of liver-cancer mortality or incidence ranging from 36 to 129. Risks were correlated with the volume of injected Thorotrast. Hemangiosarcoma, typically a very rare tumor, accounted for about one third of the tumors. The risk of leukemia, excluding chronic lymphoid leukemia, was increased 11- to 20-fold in Thorotrast-treated patients. Findings regarding mesothelioma and cancer of the extrahepatic bile duct, gallbladder, and pancreas were inconsistent across studies.

Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of thorium dioxide from studies in experimental animals. When administered by intravenous injection, thorium dioxide caused cancer of the blood vessels (hemangioendotheliosarcoma) or reticuloendothelial system (sarcoma) in the liver, spleen, and lung in rabbits; liver cancer (cholangiocellular carcinoma) in hamsters; and benign liver tumors (hepatocellular adenoma) in rats. Subcutaneous injection of thorium dioxide caused cancer at the injection site (fibrosarcoma) in rats and mice, and intraperitoneal injection caused cancer (sarcoma) in rats, mice, hamsters, rabbits, and guinea pigs (Wegener 1979, EPA 1981, IARC 2001).

Properties

Thorium dioxide is the oxide of the radioactive metallic element thorium, the second member of the actinide series of elements. Thorium-232 is the most common of the naturally occurring isotopes; it decays by emission of alpha particles and has a half-life of 1.4×10^{10} years (Hedrick 2000). The other two long-lived isotopes that decay by emission of alpha particles are thorium-230 (half-life of 77,000 years) and thorium-229 (half-life of 7,300 years). Decay products include radium-228, radium-224, and radon-220 (IARC 2001). Thorium dioxide has a molecular weight of 264 and occurs as a heavy, white crystalline powder with a melting point of 3,390°C (the highest of any metal oxide) and a boiling point of 4,400°C. It is insoluble in water and alkalis and slightly soluble in acids and biological fluids. Thorium dioxide is incandescent when heated. It is available in the United States in stocks of various particle sizes with purities ranging from 99.5% to 99.99%. The X-ray contrast medium Thorotrast is a 25% colloidal thorium dioxide suspension in aqueous dextrin (IARC 2001, Clark *et al.* 2006, HSDB 2009). Thorotrast was formerly a registered trademark of the Heyden Chemical Corporation.

Use

Thorium was discovered in 1828, and its radioactivity was discovered in 1898. In the early 1900s, the only commercial use for thorium was in gas lamp mantles. Although demand for gas mantles declined with the advent of electric lights, mantle manufacturing still accounted for 92% of thorium's non-fuel use as late as 1950 (Hedrick 2000). The use of thorium in the United States has decreased substantially because of concerns over its naturally occurring radioactivity (Hedrick 2002). Principal uses for thorium dioxide are in high-temperature ceramics, gas mantles, nuclear fuel, flame spraying, crucibles, medicines, non-silica optical glass, and thoriated tungsten filaments, and as a catalyst. It has also been used as a diagnostic aid (radiopaque medium) in feline medication (HSDB 2009).

Thorotrast was used as a contrast agent in medical radiology. It was used extensively as an intravascular contrast agent for cerebral and limb angiography in Europe, the United States, and Japan. It was also injected directly into the nasal cavity, paranasal sinus, spleen, brain, and other sites. Thorotrast treatment led to deposition of thorium and its decay products in body tissues and organs, especially reticuloendothelial tissue and bone, which resulted in continuous lifelong alpha-particle irradiation (BEIR IV 1988). Use of Thorotrast was dis-

continued in the 1950s, when harmful latent effects were observed (Grampa 1971, IARC 2001).

Production

Thorium occurs in several minerals, including monazite, thorite, huttonite, and thorogummite. Most thorium production occurs from mining of monazite as a by-product from heavy-mineral sands mined for titanium and zirconium minerals. Between 1987 and 1994, only one U.S. company produced monazite, all of which was exported. U.S. production of thorium-bearing monazite ended in the United States in 1994; since then, all U.S. production of thorium-containing products has relied on imports and existing industry and government stocks. About seven U.S. companies continue to process or fabricate various forms of thorium for non-energy uses such as described above (Hedrick 2002). In 2009, thorium dioxide was available from 12 U.S. suppliers (ChemSources 2009). From 1983 to 1987, annual U.S. imports of thorium dioxide equivalent ranged from 19.7 metric tons (43,000 lb) to 69.3 metric tons (153,000 lb) (ATSDR 1990). From 1996 to 2002, imports of thorium compounds, expressed as thorium dioxide equivalent, declined from 26,400 kg (58,200 lb) to 480 kg (1,060 lb) (Hedrick 2000, 2002). U.S. exports of thorium metal waste and scrap (thorium dioxide equivalent) from 1983 to 1987 ranged from 1.0 metric tons (2,200 lb) to 20.4 metric tons (45,000 lb) (ATSDR 1990). Between 1996 and 2002, exports of thorium compounds (thorium dioxide equivalent) ranged from a low of 58 kg (128 lb) in 1996 to a high of 5,390 kg (11,900 lb) in 2001 (Hedrick 2000, 2002). No more recent data on U.S. imports or exports were found.

Exposure

The primary routes of potential human exposure to thorium dioxide are inhalation, intravenous injection, ingestion, and dermal contact. Based on the amount of Thorotrast produced, more than 2.5 million people worldwide were exposed to thorium dioxide between 1930 and 1950 (IARC 2001). The injection dosages ranged from 2 to 70 mL of Thorotrast solution, depending on the area to be X-rayed (Sargoca *et al.* 1972). Once injected, Thorotrast is not cleared from the body, resulting in lifelong exposure (BEIR IV 1988).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, environmental releases of thorium dioxide declined from 679,129 lb in 1988 to 42,000 lb in 1993. In 1995 and 1996, 1 lb of thorium dioxide was released, and no releases were reported from 1997 to 2007 (TRI 2009). Although thorium is widespread in the environment from both natural and anthropogenic sources, concentrations in air, soil, drinking water, and foods are very low. Very few studies have investigated daily intakes of thorium in the general population; however, estimated total daily intakes of thorium-230 and thorium-232 in air, food, and water ranged from approximately 0.02 to 0.17 pCi. Higher exposures could occur among people living near hazardous-waste sites or mining areas that contain thorium (ATSDR 1990).

Occupational exposure to thorium may occur in the mining, milling, and processing of uranium, tin, rare-earth metals, and phosphate and in gas mantle manufacturing and other thorium-processing industries (ATSDR 1990, IARC 2001). Exposure could also have occurred during the formulation, packaging, preparation, or administration of thorium dioxide as a pharmaceutical.

References

- ATSDR. 1990. *Toxicological Profile for Thorium*. Agency for Toxic Substances and Disease Registry. <http://www.atsdr.cdc.gov/toxprofiles/tp147.pdf>.
- BEIR IV. 1988. *Health Risks of Radon and Other Internally Deposited Alpha-Emitters*. Biological Effects of Ionizing Radiation Series. Washington, DC: National Academy Press. 624 pp.

ChemSources. 2009. *Chem Sources - Chemical Search*. Chemical Sources International. <http://www.chemsources.com/chemonline.html> and search on thorium dioxide.

Clark DL, Neu MP, Runde W, Keogh DW. 2006. Thorium and thorium compounds. In *Kirk-Othmer Encyclopedia of Chemical Technology*, vol. 24. Online edition. New York: John Wiley & Sons. 32 pp.

Da Motta LC, da Silva Horta J, Tavares MH. 1979. Prospective epidemiological study of thorotrast-exposed patients in Portugal. *Environ Res* 18(1): 152-172.

EPA. 1981. *Chemical Hazard Information Profile. Thorium Dioxide*. Washington, DC: Office of Pesticide Programs and Toxic Substances, U.S. Environmental Protection Agency.

Faber M. 1979. Twenty-eight years of continuous follow-up of patients injected with thorotrast for cerebral angiography. *Environ Res* 18(1): 37-43.

Grampa G. 1971. Radiation injury with particular reference to thorotrast. *Pathol Annu* 6: 147-169.

Hedrick JB. 2000. Thorium. In *Minerals Yearbook, Vol 1, Minerals and Metals*. U.S. Geological Survey. <http://minerals.usgs.gov/minerals/pubs/commodity/thorium/690400.pdf>.

Hedrick JB. 2002. Thorium. In *Minerals Yearbook, Vol 1, Minerals and Metals*. U.S. Geological Survey. <http://minerals.usgs.gov/minerals/pubs/commodity/thorium/thorimyb02.pdf>.

HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. Last updated: 8/12/09. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number. Last accessed: 11/28/09.

IARC. 2001. Thorium. In *Some Internally Deposited Radionuclides*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 78. Lyon, France: International Agency for Research on Cancer. pp. 174-188.

MacMahon HE, Murphy AS, Bates MI. 1947. Endothelial-cell sarcoma of liver following Thorotrast injection. *Am. J. Pathol.* 23: 585-613.

Mori T, Maruyama T, Kato Y, Takahashi S. 1979. Epidemiological follow-up study of Japanese Thorotrast cases. *Environ Res* 18(1): 44-54.

Saragoca A, Tavares MH, Barros FB, da Silva Horta J. 1972. Some clinical and laboratory findings in patients injected with thorium dioxide. Study of 155 cases. *Am J Gastroenterol* 57(4): 301-310.

TRI. 2009. *TRI Explorer Chemical Report*. U.S. Environmental Protection Agency. <http://www.epa.gov/triexplorer> and select Thorium Dioxide.

Van Kaick G, Kaul A, Lorenz D, Muth H, Wegener K, Wesch H. 1978. Late effects and tissue dose in Thorotrast patients. Recent results of the German Thorotrast study. In *Late Biological Effects of Ionizing Radiation*, vol. 1. Vienna, Austria: International Atomic Energy Agency.

Wegener K. 1979. Systematic review of thorotrast data and facts: animal experiments. *Virchows Arch A Pathol Anat Histol* 381(3): 245-268.

Ionizing Radiation

Regulations

Department of Energy (DOE)

A comprehensive set of protection standards and program requirements has been developed for protecting individuals from ionizing radiation resulting from the conduct of DOE activities.

Radiation Dose Limits

Annual occupational dose limits for adults (the more limiting of the following): Total effective dose = 5 rem (0.05 Sv); sum of the equivalent dose to the whole body for external exposures and the committed equivalent dose to any organ or tissue other than the skin or the lens of the eye = 50 rem (0.5 Sv); eye-lens dose equivalent = 15 rem (0.15 Sv); sum of the equivalent dose to the skin or to any extremity for external exposures and the committed equivalent dose to the skin or to any extremity = 50 rem (0.5 Sv).

Dose equivalent to an embryo or fetus due to the occupational exposure of a declared pregnant woman: Shall not exceed 0.5 rem (5 mSv) during the entire pregnancy.

Annual total effective dose equivalent for individual members of the public: Shall not exceed 0.1 rem (1 mSv).

Department of Transportation (DOT)

Rules have been set governing the marking, labeling, packaging, handling, and transportation of radioactive materials.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Radionuclides are listed as hazardous air pollutants.

Emissions of radionuclides, other than radon, to the air shall not exceed those amounts that would cause any member of the public to receive in a year an effective dose \geq 10 mrem (0.1 mSv).

Emissions of radon-222 from an underground uranium mine shall not exceed the amount that would cause a member of the public to receive in a year an effective dose $>$ 10 mrem (0.1 mSv).

No source at a DOE facility shall emit into the air more than 20 pCi/m³ per sec of radon-222 as an average for the entire source.

Each stack used in the generation of phosphogypsum shall not emit more than 20 pCi/m²-sec (1.9 pCi/ft²-sec) of radon-222 into the air.

Emissions to the ambient air from an existing uranium mill tailings pile shall not exceed 20 pCi/m²-sec (1.9 pCi/ft²-sec) of radon-222.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ): range for 758 radionuclides = 0.001 to 1,000 Ci; for radon-220 and radon-222 = 0.1 Ci.

Thorium dioxide is a listed substance subject to reporting requirements.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Indoor Radon Abatement Act

Sets a long-term goal that indoor air be as free from radon as the ambient air outside buildings, and authorizes funds for radon-reduction activities.

Marine Protection, Research, and Sanctuaries Act

Ocean disposal of high-level nuclear waste is prohibited, and any request for ocean disposal of low-level waste requires a permit that must be approved by both houses of Congress.

Nuclear Waste Policy Act

Numerous containment requirements have been set that will limit the total amount of radiation entering the environment from the Yucca Mountain (Nevada) nuclear waste repository site for over 10,000 years.

Disposal systems for waste shall be designed to provide a reasonable expectation that for 10,000 years after disposal, any member of the general population in the general environment shall not receive a combined annual dose of radiation greater than 15 mrem (0.15 mSv).

Regulations have been developed to limit radiation releases from disposal systems for spent nuclear fuel of high-level or transuranic nuclear waste.

Radiation Protection Programs

Environmental radiation protection standards for nuclear power operations have been established to limit human and environmental exposure to radiation.

Resource Conservation and Recovery Act

Radioactive waste mixed with various specified hazardous wastes are prohibited from land disposal.

Safe Drinking Water Act

Maximum contaminant level (MCL) = The average annual concentration of beta particle and photon radioactivity from manmade radionuclides in drinking water must not produce an annual dose equivalent to the total body or any internal organ greater than 4 mrem (0.4 mSv).

Uranium Mill Tailings Radiation Control Act

A comprehensive set of regulations have been established to guard against exposure to radon from uranium and thorium mill tailings.

Inactive uranium processing sites shall not release radon-220 or radon-222 to the air at levels exceeding 20 pCi/m³ per sec.

Food and Drug Administration (FDA)

Rules have been established that govern ionizing radiation for the treatment of foods for human consumption and the production and processing of animal feed and pet food.

Performance standards have been set for ionizing-radiation-emitting diagnostic and therapeutic products and procedures and for accreditation and certification of facilities and personnel.

Rules have been established for use of radioactive drugs in research.

An approved new drug application is required for marketing thorium dioxide drugs.

Mine Safety and Health Administration

Regulations have been established to protect workers in underground metal and nonmetal mines against exposure to gamma radiation, including annual radiation surveys and an annual individual gamma radiation limit of 5 rem (0.05 Sv).

Regulations have been established to protect workers in underground metal and nonmetal mines against exposure to radon and radon daughters, including monitoring and record keeping requirements and various exposure limits.

Nuclear Regulatory Commission (NRC)

Comprehensive regulations have been developed to control the receipt, possession, use, transfer, and disposal of radioactive material in such a manner that the total dose to an individual does not exceed the Standards for Protection Against Radiation (see DOE Radiation Dose Limits, above). The regulations apply to entities licensed to receive, possess, use, transfer, or dispose of by-product, source, or special nuclear material or to operate a production or utilization facility, and to exposure associated with nuclear power plants and other uses of radioactive materials, including medical, veterinary, industrial, academic, and research.

Rules have been established for the medical use of radioactive material and the issuance of licenses authorizing use of the material.

Rules have been established for the packaging, preparing for shipping, and transporting of licensed radioactive material.

Rules have been established governing the receiving and storing of radioactive materials in geological repositories.

Occupational Safety and Health Administration (OSHA)

Comprehensive regulations have been set to limit worker exposure to ionizing radiation which include monitoring requirements, restricting access to areas with radiation, established exposure limits, and various precautionary procedures.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Effective dose = 50 mSv for a single year; = 20 mSv averaged over 5 years.

Annual equivalent dose = 150 mSv for the lens of the eye; = 500 mSv for the skin, hands, and feet.

Embryo-fetus exposure once the pregnancy is known: monthly equivalent dose = 0.5 mSv; dose to surface of women's abdomen for remainder of pregnancy = 2 mSv; recommended limit on intake of radionuclides = 1/20 of annual limit.

Recommended dose limit for radon daughters = 4 working level months per year (WLM/yr).

Food and Drug Administration (FDA)

Radiation protection recommendations have been established for the protection of patients from radiation during diagnostic and therapeutic procedures.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) for radon progeny in underground mines = 1 working level month (WLM) per year; average workshift concentration = 1/12 of 1 WL (0.083 WL).

A comprehensive set of recommended standards for occupational exposure to radon progeny in underground mines has been developed.

Iron Dextran Complex

CAS No. 9004-66-4

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as Infed, a registered trademark of Watson Pharma, Inc.

Carcinogenicity

Iron dextran complex is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure to iron dextran by injection caused tumors at the injection site in several species of experimental animals. Cancer at the injection site (sarcoma) was observed following administration of iron dextran complex by subcutaneous injection in mice of both sexes and in male rats and by intramuscular injection in rats and rabbits of both sexes (IARC 1973, 1982).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to iron dextran complex. There have been case reports of cancer occurring at the sites where iron dextran was thought to have been injected (IARC 1973, Greenberg 1976). Since iron dextran complex was listed in the *Second Annual Report on Carcinogens*, many epidemiological studies have evaluated the carcinogenicity of exposure to iron; however, these studies did not specifically examine exposure to iron dextran complex (Huang 2003).

Properties

Iron dextran complex is a chemical complex of iron hydroxide with dextrans, (polysaccharides that are produced by bacterial action on sugar) (IARC 1973). Iron dextran is a slightly viscous, dark reddish-brown liquid at room temperature (HSDB 2009). When used as a hematinic to treat iron-deficiency anemia in humans or animals, it is prepared as a dark-brown colloidal suspension in saline solution (IARC 1973). The veterinary product generally is more concentrated than the one intended for use in humans. Iron dextran complex is extremely soluble in water and insoluble in most organic solvents. It is unstable at higher temperatures and undergoes autoxidation between 65°C and 70°C (Akron 2009). Its shelf life is about five years.

Use

Iron dextran complex was first used in the United States in 1957. It is used for parenteral treatment of iron-deficiency anemia, but generally only in special cases, such as when oral treatment has failed. In 1960, approval to use iron dextran complex to treat iron-deficiency anemia in humans in the United States was withdrawn after studies in mice and rats demonstrated that repeated subcutaneous and intramuscular injections caused cancer at the injection site. However, in 1962, the use of iron dextran complex to treat iron-deficiency anemia in humans was reintroduced, as the risk of cancer in humans was thought to be small. Iron dextran complex is also used in veterinary medicine to treat baby pigs (IARC 1973, HSDB 2009).

Production

Iron dextran complex is produced by two manufacturers each in Europe and India and one manufacturer each in the United States and Canada (SRI 2009) and is available from six suppliers, including two in the United States (ChemSources 2009). Three products containing iron dextran complex are approved for use by the U.S. Food and Drug Administration (FDA 2009). No data on U.S. imports or exports of iron dextran were found.

Exposure

The primary routes of human exposure to iron dextran complex are intravenous or deep-intramuscular injection (IARC 1973, HSDB 2009). Iron dextran is available as an injectable product in 50-mg vials (FDA 2009). The therapeutic dose for humans is based on body weight and hemoglobin when administered for iron-deficiency anemia and on blood loss and hematocrit when given for blood loss (RxList 2010). The usual daily dose is 1 to 5 mL (50 to 250 mg of iron) (IARC 1973). Use is advised only for patients who do not respond to oral administration of iron. Before 2000, nearly all parenterally administered iron supplements were iron dextran products; however, the use of iron dextran has since diminished, while use of other iron products and the use of injectable iron supplements as a class have increased (Baillie *et al.* 2005). From 2001 to 2003, about 30 million doses of iron supplements were administered by injection, 9.3 million of which were brand-name iron dextran products (Chertow *et al.* 2006). The physician's package insert for iron dextran includes a warning of the potential for injection-site sarcoma (RxList 2010).

Occupational exposure to iron dextran complex may occur during the production, formulation, packaging, or administration of the pharmaceutical products. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 1,157 workers, including 573 women, potentially were exposed to iron dextran complex (NIOSH 1990). Exposure during production may be site-limited, because only one manufacturer of iron dextran was identified in the United States in 2009 (SRI 2009).

Regulations

Food and Drug Administration (FDA)

Iron dextran complex is a prescription drug subject to labeling and other requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

References

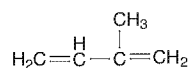
- Akron. 2009. *The Chemical Database*. The Department of Chemistry at the University of Akron. <http://uakron.edu/chem/chemsearch> and search on CAS number. Last accessed: 8/10/09.
- Baillie GR, Clark JA, Lane CE, Lane PL. 2005. Hypersensitivity reactions and deaths associated with intravenous iron preparations. *Nephrol Dial Transplant* 20(7): 1443-1449.
- ChemSources. 2009. *Chem Sources - Chemical Search*. Chemical Sources International. <http://www.chemsources.com/chemonline.html> and search on iron dextran. Last accessed: 8/10/09.
- Chertow GM, Mason PD, Vaage-Nilsen O, Ahlmen J. 2006. Update on adverse drug events associated with parenteral iron. *Nephrol Dial Transplant* 21(2): 378-382.
- FDA. 2009. *The Electronic Orange Book*. U.S. Food and Drug Administration. <http://www.fda.gov/cder/ob/default.htm> and select Search by Active Ingredient and search on iron dextran. Last accessed: 8/10/09.
- Greenberg G. 1976. Sarcoma after intramuscular iron injection. *Br Med J* 1(6024): 1508-1509.
- HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number. Last accessed: 8/10/09.
- Huang X. 2003. Iron overload and its association with cancer risk in humans: evidence for iron as a carcinogenic metal. *Mutat Res* 533(1-2): 153-171.
- IARC. 1973. Iron-carbohydrate complexes. In *Some Inorganic and Organometallic Compounds*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 2. Lyon, France: International Agency for Research on Cancer. pp. 161-178.
- IARC. 1982. Iron dextran complex. In *Chemicals, Industrial Processes and Industries Associated with Cancer in Humans*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, suppl. 4. Lyon, France: International Agency for Research on Cancer. pp. 145-146.
- NIOSH. 1990. *National Occupational Exposure Survey (1981-83)*. National Institute for Occupational Safety and Health. Last updated: 7/1/90. <http://www.cdc.gov/noes/noes1/x4721sic.html>.
- RxList. 2010. Infed. *RxList: The Internet Drug Index*. <http://www.rxlist.com/infed-drug.htm>. Last accessed 1/6/10.
- SRI. 2009. *Directory of Chemical Producers*. Menlo Park, CA: SRI Consulting. Database edition. Last accessed: 8/10/09.

Isoprene

CAS No. 78-79-5

Reasonably anticipated to be a human carcinogen

First listed in the *Ninth Report on Carcinogens* (2000)



Carcinogenicity

Isoprene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure to isoprene by inhalation caused tumors at several different tissue sites in mice and rats. In mice of both sexes, isoprene caused blood-vessel cancer (hemangiosarcoma) and benign or malignant tumors of the Harderian gland (adenoma or carcinoma) and the lung (alveolar/bronchiolar adenoma or carcinoma). In male mice, it also caused cancer of the hematopoietic system (histiocytic sarcoma) and benign or malignant tumors of the liver (hepatocellular adenoma or carcinoma) and forestomach (squamous-cell papilloma or carcinoma). In rats of both sexes, isoprene caused benign or malignant tumors of the mammary gland (fibroadenoma or carcinoma) and kidney (renal-cell adenoma or carcinoma). In male rats, it also caused benign tumors of the testis (adenoma) (NTP 1995, Placke *et al.* 1996, Melnick and Sills 2001).

Studies on Mechanisms of Carcinogenesis

Isoprene is the 2-methyl analog of 1,3-butadiene, an industrial chemical that has been identified as a carcinogen in humans and experimental animals (Gervasi *et al.* 1985, NTP 1999a,b). The isoprene analogue isopentenyl pyrophosphate is a building block of cholesterol synthesis, and levels of exhaled isoprene correlate with cholesterol

synthesis (IARC 1994, Rieder *et al.* 2001). Isoprene and butadiene are metabolized to monoepoxide and diepoxide intermediates by liver microsomal cytochrome P450-dependent monooxygenases from several species, including humans (Gervasi *et al.* 1985, IARC 1994, NTP 1999a). These intermediates may be detoxified by hydrolysis (catalyzed by epoxide hydrolase) or conjugation with glutathione (catalyzed by glutathione S-transferase).

The diepoxide intermediates of isoprene and butadiene caused mutations in *Salmonella typhimurium*, whereas the monoepoxides of isoprene and parent compounds did not. In mammalian cells *in vitro*, isoprene did not cause sister chromatid exchange, chromosomal aberrations, or micronucleus formation (NTP 1995, 1999a), but did cause DNA damage in human peripheral-blood mononuclear cells and human leukemia cells when incubated with microsomal enzymes (Fabiani *et al.* 2007). In mice exposed *in vivo*, isoprene and 1,3-butadiene caused sister chromatid exchange in bone-marrow cells and micronucleus formation in peripheral-blood erythrocytes (Tice 1988, Tice *et al.* 1988). Sites at which both isoprene and butadiene caused tumors in rodents include the liver, lung, Harderian gland, forestomach, hematopoietic tissue, and circulatory system in mice and the mammary gland, kidney, and testis in rats (NTP 1999a,b). Harderian-gland tumors caused by isoprene in mice had a high frequency of unique mutations of the *K-ras* protooncogene (A to T transversions at codon 61) (Hong *et al.* 1997).

There is no evidence to suggest that mechanisms by which isoprene causes tumors in experimental animals would not also operate in humans.

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to isoprene.

Properties

Isoprene is structurally similar to 1,3-butadiene and exists as a colorless, volatile liquid at room temperature (NTP 1999a). It occurs frequently in nature and is emitted to the environment by plants and trees. Isoprene is practically insoluble in water, but is soluble in ethanol, diethyl ether, benzene, and acetone. It is stable under normal conditions, but it is very flammable and will polymerize vigorously or decompose with abrupt changes in temperature or pressure (IARC 1994, Akron 2009). Physical and chemical properties of isoprene are listed in the following table.

Property	Information
Molecular weight	68.1
Specific gravity	0.681 at 20°C/4°C
Melting point	-145.95°C
Boiling point	34.07°C at 760 mm Hg
Log <i>K</i> _{ow}	2.42
Water solubility	0.642 g/L at 25°C
Vapor pressure	550 mm Hg at 25°C
Vapor density relative to air	2.4

Source: HSDB 2009.

Use

The majority of isoprene produced commercially is used to make synthetic rubber (*cis*-polyisoprene), most of which is used to produce vehicle tires. The second- and third-largest uses are in the production of styrene-isoprene-styrene block polymers and butyl rubber (isobutene-isoprene copolymer) (IARC 1994).

Production

Isoprene is recovered as a by-product of thermal cracking of naphtha or gas oil from *C*₅ streams (IARC 1994, NTP 1999a). The isoprene

yield is about 2% to 5% of the ethylene yield. U.S. demand for isoprene grew 6.5% annually from 1985 to 1992 (NTP 1999a). In 1994, isoprene production in the United States was about 619 million pounds, almost 29% more than in 1992. Estimated isoprene production capacity for eight facilities was 598 million pounds in 1996, based on estimates of isoprene content of product stream available from ethylene production via heavy liquids. In 2009, isoprene was produced by 22 manufacturers worldwide, including 12 U.S. producers (SRI 2009), and was available from 23 suppliers, including 12 U.S. suppliers (ChemSources 2009). U.S. imports of isoprene (purity $\geq 95\%$ by weight) increased from zero in 1989 to a peak of 144 million pounds in 2003. Imports declined to 19.6 million pounds in 2004, the lowest level since 1992, but remained near 32 million pounds from 2005 through 2008. During this period, U.S. exports of isoprene ranged from 7.9 million to 39.6 million pounds (in 2006) (USITC 2009). Reports filed from 1986 to 2002 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of isoprene totaled 100 million to 500 million pounds (EPA 2004).

Exposure

Isoprene is formed endogenously in humans at a rate of $0.15 \mu\text{mol/kg}$ of body weight per hour, equivalent to approximately 2 to 4 mg/kg per day (Taalman 1996), and is the major hydrocarbon in human breath (accounting for up to 70% of exhaled hydrocarbons) (Gelmont *et al.* 1981). Concentrations in human blood range from 1.0 to 4.8 $\mu\text{g/L}$ (Cailleux *et al.* 1992). Isoprene is produced at higher rates in males than females. The rate of isoprene production increases with age up to the age of 29 (Lechner *et al.* 2006); it is lower in young children than adults by a factor of about 2.4 (Taucher *et al.* 1997). In a study of 30 adult volunteers, the mean isoprene concentration measured in alveolar breath was 118 ppb, with a range of 0 to 474 ppb (Turner *et al.* 2006). After 20 to 30 minutes of exercise, isoprene concentration in exhaled air decreased to a range of 0 to 40 ppb (Senthilmohan *et al.* 2000). Smoking one cigarette increased the concentration of isoprene in exhaled air by 70% (Senthilmohan *et al.* 2001). Isoprene is also produced endogenously by other animals. Production rates reported for rats and mice were 1.9 and 0.4 $\mu\text{mol/kg}$ of body weight per hour, respectively (Peter *et al.* 1987).

Foods of plant origin would be expected to be a source of daily exposure to isoprene, since isoprene is emitted by agricultural crops and is the basic structural unit in countless natural products found in foods, such as terpenes and vitamins A and K (NTP 1999a). Isoprene has been reported to occur in the essential oil of oranges, the fruit of hops, carrot roots, and roasted coffee (Taalman 1996, NTP 1999a).

Isoprene is emitted from plants and trees and is present in the general environment at low concentrations (Taalman 1996). Isoprene emissions from many types of plants have been estimated under various climatic conditions, to evaluate their importance in global climate change (Mayrhofer *et al.* 2004, Parra *et al.* 2004, Schnitzler *et al.* 2004, 2005, Pegoraro *et al.* 2005, Sasaki *et al.* 2005, Sharkey 2005, Moukhtar *et al.* 2006, Simon *et al.* 2006, Tambunan *et al.* 2006). Annual global isoprene emissions, estimated at 175 billion to 503 billion kilograms (386 billion to 1,109 billion pounds), account for an estimated 57% of total global natural volatile organic compound emissions (Guenther *et al.* 1995). The average biogenic emission rate factor for isoprene in U.S. woodlands is 3 mg/m^2 per hour (compared with 5.1 mg/m^2 for total volatile organic compounds) (Guenther *et al.* 1994). Isoprene concentrations in biogenic emissions range from 8% to 91% of total volatile organic compounds, averaging 58%. Because isoprene biosynthesis is associated with photosynthesis, isoprene emissions are negligible at night (Lamb *et al.* 1993). Because isoprene is emitted

primarily by deciduous trees, emissions are seasonal, being highest in the summer and lowest in the winter (Guenther *et al.* 1994, Fuentes and Wang 1999). The south central and southeastern areas of the United States have the highest biogenic emissions (Lamb *et al.* 1993, Guenther *et al.* 1994). The half-life of atmospheric isoprene has been estimated at 0.5 hours by reaction with nitric oxide, 4 hours by reaction with hydroxyl radicals, and 19 hours by reaction with ozone (HSDB 2009).

Anthropogenic sources of isoprene in the atmosphere include ethylene production by cracking naphtha, wood pulping, oil fires, wood-burning stoves and fireplaces, other biomass combustion, tobacco smoking (200 to 400 μg per cigarette), gasoline, and exhaust from turbines and automobiles (Adam *et al.* 2006, HSDB 2009). Isoprene has been measured as one of the volatile organic compounds in the ambient air in regions with industrial pollution, and in urban, residential, and rural areas as an indicator of the potential for ozone formation. Thus, isoprene is a key indicator for regional air quality, as well as being a component of the global carbon cycle (Borbon *et al.* 2004, Guo *et al.* 2004, Kuster *et al.* 2004, Warneke *et al.* 2005, Helten *et al.* 2006).

The reported concentration of isoprene in U.S. ambient air ranges from 1 to 21 parts per billion carbon (ppbC) and generally is less than 10 ppbC. Isoprene accounts for less than 10% of non-methane hydrocarbons in ambient air. Biogenic hydrocarbons may contribute more to total atmospheric hydrocarbons under stagnant atmospheric conditions (Altschuller 1983, Hagerman *et al.* 1997). The major sources of isoprene in ambient air appear to be biogenic emissions at rural sites and vehicular emissions in urban areas (Borbon *et al.* 2001, So and Wang 2004). Where the source is primarily biogenic, the isoprene concentration slowly increases during the day, reaching a peak in the middle of the day, when photosynthesis is greatest. Where vehicular emissions are the primary source, the isoprene concentration peaks during the morning and evening rush hours and is low in the middle of the day (Borbon *et al.* 2002). One study concluded that in summer, at least 80% of the isoprene at a rural site was due to biogenic emissions, but that in winter, more than 90% of residual isoprene was from urban air-mass mixing (Borbon *et al.* 2004). Where industrial emissions are the primary source of isoprene, the concentration may peak at night, or there may be no peak at all (Zhao *et al.* 2004, Chiang *et al.* 2007).

The primary source of isoprene in indoor air is environmental tobacco smoke. Isoprene was found to be the major component of hydrocarbons in the air of a smoky café (10 patrons smoking, 10 not smoking) (16.7%) and in sidestream smoke (29.2%) (Barrefors and Petersson 1993). A monitoring survey in November 1992 in homes and workplaces in the greater Philadelphia area found mean isoprene concentrations in personal air samples of 4.65 $\mu\text{g/m}^3$ in 60 nonsmoking homes, 18.15 $\mu\text{g/m}^3$ in 29 homes with smokers, 5.29 $\mu\text{g/m}^3$ in 51 nonsmoking workplaces, and 22.80 $\mu\text{g/m}^3$ in 28 workplaces that allowed smoking (Heavner 1996). A survey in the Lower Rio Grande Valley of Texas reported a median summertime isoprene concentration of 2.90 $\mu\text{g/m}^3$ for three indoor air samples (it was not reported whether the occupants were smokers or nonsmokers), compared with 0.40 $\mu\text{g/m}^3$ for three outdoor air samples (Mukerjee 1997).

Air-monitoring data were collected at three U.S. facilities that produced isoprene monomers or polymers; 98.5% of the samples showed concentrations of less than 10 ppm, and 91.3% of less than 1 ppm (Leber 2001, Lynch 2001). The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 58,000 workers in over 30 industries potentially were exposed to isoprene (NIOSH 1976). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated in a more limited survey that 3,700 workers

in four industries, including 578 women, potentially were exposed to isoprene (NIOSH 1990).

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of isoprene on ships and barges.

Department of Transportation (DOT)

Isoprene is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

New Source Performance Standards: Manufacture of isoprene is subject to certain provisions for the control of volatile organic compound emissions.

Prevention of Accidental Release: Threshold quantity (TQ) = 10,000 lb.

Clean Water Act

Isoprene has been designated a hazardous substance.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb.

References

- Adam T, Mitschke S, Streibel T, Baker RR, Zimmermann R. 2006. Quantitative puff-by-puff-resolved characterization of selected toxic compounds in cigarette mainstream smoke. *Chem Res Toxicol* 19(4): 511-520.
- Akron. 2009. *The Chemical Database*. The Department of Chemistry at the University of Akron. <http://uakron.edu/chem> and search on CAS number. Last accessed: 7/7/09.
- Altschuller A. 1983. Natural volatile organic substances and their effect on air quality in the United States. *Atmos Environ* 17(11): 2131-2165.
- Barrefors G, Petersson G. 1993. Assessment of ambient volatile hydrocarbons from tobacco smoke and from vehicle emissions. *J Chromatogr* 643(1-2): 71-76.
- Borbon A, Fontaine H, Veillerot M, Locoge N, Galloo JC, Guillermo R. 2001. An investigation into the traffic-related fraction of isoprene at an urban location. *Atmos Environ* 35(22): 3749-3760.
- Borbon A, Locoge N, Veillerot M, Galloo JC, Guillermo R. 2002. Characterisation of NMHCs in a French urban atmosphere: overview of the main sources. *Sci Total Environ* 292(3): 177-191.
- Borbon A, Coddeville P, Locoge N, Galloo JC. 2004. Characterising sources and sinks of rural VOC in eastern France. *Chemosphere* 57(8): 931-942.
- Cailleux A, Cognny M, Allain P. 1992. Blood isoprene concentrations in humans and in some animal species. *Biochem Med Metab* 47(2): 157-160.
- ChemSources. 2009. *Chem Sources - Chemical Search*. Chemical Sources International. <http://www.chemsources.com/chemonline.html> and search on isoprene. Last accessed: 7/7/09.
- Chiang HL, Tsai JH, Chen SY, Lin KH, Ma SY. 2007. VOC concentration profiles in an ozone non-attainment area: A case study in an urban and industrial complex metroplex in southern Taiwan. *Atmos Environ* 41(9): 1848-1860.
- EPA. 2004. *Non-confidential IUR Production Volume Information*. U.S. Environmental Protection Agency. <http://www.epa.gov/oppt/iur/tools/data/2002-vol.html> and search on CAS number.
- Fabiani R, Rosignoli P, De Bartolomeo A, Fucelli R, Morozzi G. 2007. DNA-damaging ability of isoprene and isoprene mono-epoxide (EPOX I) in human cells evaluated with the comet assay. *Mutat Res* 629(1): 7-13.
- Fuentes JD, Wang D. 1999. On the seasonality of isoprene emissions from a mixed temperate forest. *Ecol Appl* 9(4): 1118-1131.
- Gelmont D, Stein RA, Mead JF. 1981. Isoprene—the main hydrocarbon in human breath. *Biochem Biophys Res Commun* 99(4): 1456-1460.
- Gervasi PG, Citti L, Del Monte M. 1985. Mutagenicity and chemical reactivity of epoxidic intermediates of the isoprene metabolism and other structurally related compounds. *Mutat Res* 156(1-2): 77-82.
- Guenther A, Zimmerman P, Wildermuth M. 1994. Natural volatile organic-compound emission rate estimates for U.S. woodland landscapes. *Atmos Environ* 28(6): 1197-1210.
- Guenther A, Hewitt CN, Erickson D, Fall R, Geron C, Graedel T, et al. 1995. A global model of natural volatile organic compound emissions. *J Geophys Res—Atmos* 100(D5): 8873-8892.
- Guo H, Lee SC, Louie PK, Ho KF. 2004. Characterization of hydrocarbons, halocarbons and carbonyls in the atmosphere of Hong Kong. *Chemosphere* 57(10): 1363-1372.
- Hagerman LM, Aneja VP, Lonneman WA. 1997. Characterization of non-methane hydrocarbons in the rural southeast United States. *Atmos Environ* 31(23): 4017-4038.
- Heavner DL. 1996. Determination of volatile organic compounds and respirable suspended particulate matter in New Jersey and Pennsylvania homes and workplaces. *Environ Int* 22(2): 159-183.
- Hellen H, Hakola H, Pirjola L, Laurila T, Pystynen KH. 2006. Ambient air concentrations, source profiles, and source apportionment of 71 different C₂-C₁₀ volatile organic compounds in urban and residential areas of Finland. *Environ Sci Technol* 40(1): 103-108.
- Hong HL, Devereux TR, Melnick RL, Eldridge SR, Greenwell A, Haseman J, Boorman GA, Sills RC. 1997. Both K-ras and H-ras protooncogene mutations are associated with Harderian gland tumorigenesis in B6C3F₁ mice exposed to isoprene for 26 weeks. *Carcinogenesis* 18(4): 783-789.
- HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number. Last accessed: 7/7/09.
- IARC. 1994. Isoprene. In *Some Industrial Chemicals*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 60. Lyon, France: International Agency for Research on Cancer. pp. 215-232.
- Kuster WC, Jobson BT, Karl T, Riemer D, Apel E, Goldan PD, Fehsenfeld FC. 2004. Intercomparison of volatile organic carbon measurement techniques and data at La Porte during the TexAQ52000 Air Quality Study. *Environ Sci Technol* 38(1): 221-228.
- Lamb B, Gay D, Westberg H, Pierce T. 1993. A biogenic hydrocarbon emission inventory for the U.S.A. using a simple forest canopy model. *Atmos Environ Part A—Gen Top* 27(11): 1673-1690.
- Leber AP. 2001. Overview of isoprene monomer and polyisoprene production processes. *Chem Biol Interact* 135-136: 169-173.
- Lechner M, Moser B, Niederseer D, Karlseder A, Holzknecht B, Fuchs M, Colvin S, Tilg H, Rieder J. 2006. Gender and age specific differences in exhaled isoprene levels. *Respir Physiol Neurobiol* 154(3): 478-483.
- Lynch J. 2001. Occupational exposure to butadiene, isoprene and chloroprene. *Chem Biol Interact* 135-136: 207-214.
- Mayrhofer S, Heizmann U, Magel E, Eiblmeier M, Müller A, Renneberg H, Hampp R, Schnitzler JP, Kreuzwieser J. 2004. Carbon balance in leaves of young poplar trees. *Plant Biol* 6(6): 730-739.
- Melnick RL, Sills RC. 2001. Comparative carcinogenicity of 1,3-butadiene, isoprene, and chloroprene in rats and mice. *Chem Biol Interact* 135-136: 27-42.
- Moukhtar S, Couret C, Rouil L, Simon V. 2006. Biogenic volatile organic compounds (BVOCs) emissions from *Abies alba* in a French forest. *Sci Total Environ* 354(2-3): 232-245.
- Mukerjee S. 1997. An environmental scoping study in the lower Rio Grande Valley of Texas—III. Residential microenvironmental monitoring for air, house dust, and soil. *Environ Int* 23(5): 657-673.
- NIOSH. 1976. *National Occupational Hazard Survey (1972-74)*. DHEW (NIOSH) Publication No. 78-114. Cincinnati, OH: National Institute for Occupational Safety and Health.
- NIOSH. 1990. *National Occupational Exposure Survey (1981-83)*. National Institute for Occupational Safety and Health. Last updated: 7/1/90. <http://www.cdc.gov/noes/noes1/40940sic.html>
- NTP. 1995. *NTP Technical Report on the Toxicity Studies of Isoprene (CAS No. 78-79-5) Administered by Inhalation to F344/N Rats and B6C3F₁ Mice*. NTP Technical Report Series no. 31. Research Triangle Park, NC: National Toxicology Program. pp. 1-65.
- NTP. 1999a. *NTP Report on Carcinogens Background Document for Isoprene*. National Toxicology Program. <http://ntp.niehs.nih.gov/files/isoprene.pdf>.
- NTP. 1999b. *NTP Toxicology and Carcinogenesis Studies of Isoprene (CAS No. 78-79-5) in F344/N Rats (Inhalation Studies)*. NTP Technical Report Series no. 486. Research Triangle Park, NC: National Toxicology Program. 178 pp.
- Parra R, Gasso S, Baldasano JM. 2004. Estimating the biogenic emissions of non-methane volatile organic compounds from the North Western Mediterranean vegetation of Catalonia, Spain. *Sci Total Environ* 329(1-3): 241-259.
- Pegoraro E, Rey A, Barron-Gafford G, Monson R, Malhi Y, Murthy R. 2005. The interacting effects of elevated atmospheric CO₂ concentration, drought and leaf-to-air vapour pressure deficit on ecosystem isoprene fluxes. *Oecologia* 146(1): 120-129.
- Peter H, Wiegand HJ, Bolt HM. 1987. Pharmacokinetics of isoprene in mice and rats. *Toxicol Lett* 36(1): 9-14.
- Placke ME, Griffis L, Bird M, Bus J, Persing RL, Cox LA Jr. 1996. Chronic inhalation oncogenicity study of isoprene in B6C3F₁ mice. *Toxicology* 113(1-3): 253-262.
- Rieder J, Lirk P, Ebenbichler C, Gruber G, Prazeller P, Lindinger W, Amann A. 2001. Analysis of volatile organic compounds: possible applications in metabolic disorders and cancer screening. *Wien Klin Wochenschr* 113(5-6): 181-185.
- Sasaki M, Nakamura Y, Fujita K, Kinugawa Y, Iida T, Urahama Y. 2005. Relation between phase structure and peel adhesion of poly(styrene-isoprene-styrene) triblock copolymer/tackifier blend system. *J Adhes Sci Technol* 19(16): 1445-1457.
- Schnitzler JP, Graus M, Kreuzwieser J, Heizmann U, Renneberg H, Wisthaler A, Hansel A. 2004. Contribution of different carbon sources to isoprene biosynthesis in poplar leaves. *Plant Physiol* 135(1): 152-160.
- Schnitzler JP, Zimmer I, Bachl A, Arend M, Fromm J, Fischbach RJ. 2005. Biochemical properties of isoprene synthase in poplar (*Populus x canescens*). *Planta* 222(5): 777-786.
- Senthilmohan ST, Milligan DB, McEwan MJ, Freeman CG, Wilson PF. 2000. Quantitative analysis of trace gases of breath during exercise using the new SIFT-MS technique. *Redox Rep* 5(2-3): 151-153.
- Senthilmohan ST, McEwan MJ, Wilson PF, Milligan DB, Freeman CG. 2001. Real time analysis of breath volatiles using SIFT-MS in cigarette smoking. *Redox Rep* 6(3): 185-187.
- Sharkey TD. 2005. Effects of moderate heat stress on photosynthesis: Importance of thylakoid reactions, rubisco deactivation, reactive oxygen species, and thermotolerance provided by isoprene. *Plant Cell Environ* 28(3): 269-277.
- Simon V, Dumergues L, Ponche JL, Torres L. 2006. The biogenic volatile organic compounds emission inventory in France: application to plant ecosystems in the Berre-Marseilles area (France). *Sci Total Environ* 372(1): 164-182.
- So KL, Wang T. 2004. C₃-C₁₂ non-methane hydrocarbons in subtropical Hong Kong: spatial-temporal variations, source-receptor relationships and photochemical reactivity. *Sci Total Environ* 328(1-3): 161-174.

SRI. 2009. *Directory of Chemical Producers*. Menlo Park, CA: SRI Consulting. Database edition. Last accessed: 7/13/09.

Taalman R. 1996. Isoprene: Background and issues. *Toxicology* 113(1-3): 242-246.

Tambunan P, Baba S, Kuniyoshi A, Iwasaki H, Nakamura T, Yamasaki H, Oku H. 2006. Isoprene emission from tropical trees in Okinawa Island, Japan. *Chemosphere* 65(11): 2138-2144.

Taucher J, Hansel A, Jordan A, Fall R, Futrell JH, Lindinger W. 1997. Detection of isoprene in expired air from human subjects using proton-transfer-reaction mass spectrometry. *Rapid Commun Mass Spectrom* 11(11): 1230-1234.

Tice RR. 1988. The cytogenetic evaluation of *in vivo* genotoxic and cytotoxic activity using rodent somatic cells. *Cell Biol Toxicol* 4(4): 475-486.

Tice RR, Boucher R, Luke CA, Paquette DE, Melnick RL, Shelby MD. 1988. Chloroprene and isoprene: cytogenetic studies in mice. *Mutagenesis* 3(2): 141-146.

Turner C, Spanel P, Smith D. 2006. A longitudinal study of breath isoprene in healthy volunteers using selected ion flow tube mass spectrometry (SIFT-MS). *Physiol Meas* 27(1): 13-22.

USITC. 2009. *USITC Interactive Tariff and Trade DataWeb*. United States International Trade Commission. http://dataweb.usitc.gov/scripts/user_set.asp and search on HTS no. 2901242000. Last accessed: 7/7/09.

Warneke C, Kato S, De Gouw JA, Goldan PD, Kuster WC, Shao M, Lovejoy ER, Fall R, Fehsenfeld FC. 2005. Online volatile organic compound measurements using a newly developed proton-transfer ion-trap mass spectrometry instrument during New England Air Quality Study—Intercontinental Transport and Chemical Transformation 2004: performance, intercomparison, and compound identification. *Environ Sci Technol* 39(14): 5390-5397.

Zhao WX, Hopke PK, Karl T. 2004. Source identification of volatile organic compounds in Houston, Texas. *Environ Sci Technol* 38(5): 1338-1347.

humidity at room temperature (Akron 2009). Physical and chemical properties of chlordecone are listed in the following table.

Property	Information
Molecular weight	490.6 ^a
Specific gravity	1.59 to 1.63 at 25°C ^a
Melting point	350°C (decomposes) ^a
Boiling point	434°C ^b
Log <i>K</i> _{ow}	5.41 ^a
Water solubility	2.70 mg/L 25°C ^a
Vapor pressure	2.25 × 10 ⁻⁷ mm Hg at 25°C ^a
Vapor density relative to air	16.94 ^a

Sources: ^aHSDB 2009, ^bAkron 2009.

Use

Chlordecone was first introduced as a pesticide in 1958 and was used until 1978, when its use in the United States was discontinued (NCI 1976, IARC 1979, HSDB 2009). Chlordecone was used as an insecticide for leaf-eating insects, ants, and cockroaches, as a larvicide for flies, and for control of insects that attack structures. Chlordecone was also used on bananas, non-bearing citrus trees, tobacco, ornamental shrubs, lawns, turf, and flowers.

Production

Total U.S. production of chlordecone from 1951 to 1975 was estimated at 3.6 million pounds (ATSDR 1995). Annual production at one plant in Hopewell, Virginia, reached a peak of over one million pounds per year in 1974; production ceased in July 1975 by order of the State of Virginia (Huggett and Bender 1980). Between 90% and 99% of total chlordecone production was exported to Europe, Asia, Latin America, and Africa (ATSDR 1995). In 2009, no producers of chlordecone were identified (SRI 2009), but chlordecone was available from eight U.S. suppliers and one European supplier (ChemSources 2009).

Exposure

The primary routes of potential human exposure to chlordecone are inhalation, ingestion, and dermal contact. Chlordecone is very stable in the environment, and no degradation products have been identified. It adsorbs to particulate matter in the air, water, and soil and is removed from the atmosphere and water column by deposition and settling and from the surface soil by erosion (ATSDR 1995). When released to air, chlordecone will not directly photodegrade or react with photochemically produced hydroxyl radicals (HSDB 2009). When released to water, chlordecone adsorbs to sediment and over time is buried by sediment accumulation (Huggett and Bender 1980). Its half-life in a model river is 3.8 to 46 years (HSDB 2009). Chlordecone bioaccumulates in fish and crustaceans (Carver and Griffith 1979). When released to soil, chlordecone will adsorb to soil particles; some leaching to groundwater may occur.

In the United States, detectable levels of chlordecone were found in 400 samples of air, drinking water, plant and aquatic organisms, and municipal waste where chlordecone was manufactured (ATSDR 1995). Chlordecone has also been measured in the particulate matter and sediment in rivers on the island of Martinique in 2002 at concentrations of up to 57 µg/kg (Bocquene and Franco 2005). Bananas are the major crop in Martinique, and chlordecone was frequently used as an insecticide on banana plantations.

Concentrations of chlordecone in the environment near the Hopewell manufacturing site were 1% to 40% in dust collected one block from the plant, 1% to 2% in soil adjacent to the plant, and 2 to 6 ppm in soil at a distance of 1,000 meters from the plant (Luellen *et al.* 2006). Very high concentrations of chlordecone were detected in effluent from the Hopewell plant (0.1 to 1.0 mg/L) and in water from

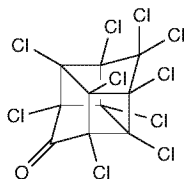
Kepone

CAS No. 143-50-0

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Kepone was formerly a registered trademark of the Allied Chemical Corporation; also known as chlordecone



Carcinogenicity

Kepone (chlordecone) is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Dietary administration of chlordecone caused liver cancer (hepatocellular carcinoma) in rats and mice of both sexes. In addition, the time to detection of the first hepatocellular carcinoma observed at death was shorter in male mice exposed to chlordecone than in unexposed controls and appeared to be inversely related to exposure level in mice and rats of both sexes (NCI 1976, IARC 1979).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to chlordecone.

Properties

Chlordecone is a chlorinated polycyclic ketone that is an odorless, colorless-to-tan crystal at room temperature (HSDB 2009). It is practically insoluble in water, soluble in acetone, alcohols, ketones, and acetic acid, and less soluble in benzene and light petroleum. Chlordecone is stable to about 350°C but readily hydrates on exposure to

the plant's holding ponds (2 to 3 mg/L). However, over time, concentrations in the James River (adjacent to the plant) have fallen dramatically due to settling of chlordecone and its eventual burial in sediment (Huggett and Bender 1980). Concentrations of chlordecone in bed sediments of the James River between 1976 and 1978 ranged from undetectable ($\leq 0.01 \mu\text{g/g}$) to $5 \mu\text{g/g}$ (ATSDR 1995). Chlordecone concentrations in finfish in the James River in the 1980s reached a steady state below the action level of $0.3 \mu\text{g/g}$; however, 94% of the fish sampled since 1987 had detectable chlordecone concentrations ($\geq 0.01 \mu\text{g/g}$). Fishing restrictions remained in effect until 1989, when restrictions as a result of chlordecone contamination were removed; however, a Virginia Department of Health fish consumption advisory remained in effect as of 2006 (Luellen *et al.* 2006).

Chlordecone is also a degradation product of another insecticide, mirex (IARC 1979). Investigators have detected chlordecone in soil at a concentration of $0.02 \mu\text{g/g}$ of soil 12 years after mirex was applied at the rate of $1 \mu\text{g/g}$ of soil. Additional exposure information may be found in the Agency for Toxic Substances and Disease Registry's *Toxicological Profile for Mirex and Chlordecone* (ATSDR 1995).

At the time production ceased (in July 1975), half of the workers at the Hopewell manufacturing facility exhibited neurological symptoms. Chlordecone was measured in the blood of these exposed workers at levels of up to $11.8 \mu\text{g/mL}$. In 1976, the National Institute for Occupational Safety and Health identified 50 facilities that processed or formulated pesticides using chlordecone and estimated that about 600 U.S. workers potentially were exposed to chlordecone (NIOSH 1976).

Regulations

Environmental Protection Agency (EPA)

Comprehensive Environmental Response, Compensation, and Liability Act
Reportable quantity (RQ) = 1 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of chlordecone = U142.

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

Action levels for chlordecone in fish, shellfish, and crabmeat range from 0.3 to 0.4 ppm.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 0.001 mg/m^3 .

Listed as a potential occupational carcinogen.

References

- Akron. 2009. *The Chemical Database*. The Department of Chemistry at the University of Akron. <http://uakron.edu/chem/erd> and search on CAS number. Last accessed: 7/7/09.
- ATSDR. 1995. *Toxicological Profile for Mirex and Chlordecone*. Agency for Toxic Substances and Disease Registry. <http://www.atsdr.cdc.gov/toxprofiles/tp66.pdf>.
- Bocquene G, Franco A. 2005. Pesticide contamination of the coastline of Martinique. *Mar Pollut Bull* 51(5-7): 612-619.
- Carver RA, Griffith FD Jr. 1979. Determination of kepone dechlorination products in finfish, oysters, and crustaceans. *J Agric Food Chem* 27(5): 1035-1037.
- ChemSources. 2009. Chemical Sources International. <http://www.chemsources.com/chemonline.html> and search on chlordecone. Last accessed: 7/7/09.
- HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number. Last accessed: 7/7/09.
- Huggett RJ, Bender ME. 1980. Kepone in the James River. *Environ Sci Technol* 14(8): 918-923.
- IARC. 1979. Chlordecone. In *Some Halogenated Hydrocarbons*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 20. Lyon, France: International Agency for Research on Cancer. pp. 67-81.
- Luellen DR, Vadas GG, Unger MA. 2006. Kepone in James River fish: 1976-2002. *Sci Total Environ* 358(1-3): 286-297.

NCI. 1976. *Report on the Carcinogenesis Bioassay of Technical Grade Chlordecone (Kepone)*. National Cancer Institute. <http://pubs.access.gpo.gov/GPO/LPS59010>.

NIOSH. 1976. *Recommended Standard for Occupational Exposure to Kepone*. National Institute for Occupational Safety and Health. <http://www.cdc.gov/niosh/pdfs/76-kepon.pdf>.

SRI. 2009. *Directory of Chemical Producers*. Menlo Park, CA: SRI Consulting. Database edition. Last accessed: 7/7/09.

Lead and Lead Compounds

CAS No. 7439-92-1 (Lead)

No separate CAS No. assigned for lead compounds as a class

Reasonably anticipated to be human carcinogens

First listed in the *Eleventh Report on Carcinogens* (2004)

Also known as Pb

Introduction

The compounds lead phosphate and lead acetate were first listed in the *Second Annual Report on Carcinogens* in 1981 as *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity in experimental animals. The listing of lead and lead compounds supersedes the previous listing of lead phosphate and lead acetate in the *Report on Carcinogens* and applies to lead and all lead compounds.

Carcinogenicity

Lead and lead compounds are *reasonably anticipated to be human carcinogens* based on limited evidence of carcinogenicity from studies in humans and sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Humans

Lead exposure has been associated with increased risk of lung, stomach, and urinary-bladder cancer in diverse human populations (Fu and Boffetta 1995, Steenland and Boffetta 2000, NTP 2003). The strongest epidemiological evidence is for lung and stomach cancer, which are consistently but weakly associated with occupations and industries entailing lead exposure and with indices of individual lead exposure, including job history and biological monitoring of occupationally exposed and general populations. However, most studies of lead exposure and cancer reviewed had limitations, including poor exposure assessment and failure to control for confounding by other factors that could increase the risk of cancer (such as lifestyle factors and concurrent occupational exposure to other carcinogens), and did not demonstrate relationships between the level or duration of exposure and the magnitude of cancer risk. The crude exposure measures used in most studies, such as treating whole plants or occupations as having uniform exposure, may have limited the magnitude of risk estimates, most of which were modest. Evidence from epidemiological studies therefore is compatible with small increases in the risk of lung or stomach cancer; however, this evidence must be weighed against the potential for confounding by factors such as smoking, diet, or coexposure to arsenic.

Cancer Studies in Experimental Animals

Lead compounds caused tumors in several species of experimental animals, at several different tissue sites, and by several different routes of exposure. Carcinogenicity was observed in studies with inorganic lead compounds, both soluble (lead acetate and lead subacetate) and insoluble (lead phosphate, lead chromate), and with tetraethyl lead (an organic lead compound). Lead caused cancer in rats and/or mice exposed orally, by injection, or perinatally (via the pla-

centa or lactation). Benign and malignant kidney tumors (adenoma, carcinoma, and adenocarcinoma) were most frequently associated with lead exposure, and tumors of the brain, hematopoietic system, and lung were reported in some studies (IARC 1980, 1987).

Lead subacetate administered in the diet caused benign and malignant kidney tumors (adenoma and carcinoma or adenocarcinoma) in mice and rats of both sexes and brain tumors (glioma) in rats, and its administration by intraperitoneal injection caused benign lung tumors (adenoma) in mice. Lead acetate administered in the diet or drinking water caused benign and malignant kidney tumors (adenoma and carcinoma) in rats and increased the incidence of virus-induced lymphocytic leukemia in mice. After pregnant mice were given lead acetate in the drinking water from gestation day 12 to four weeks postpartum, the offspring showed a dose-related increase in proliferative lesions of the kidneys (including atypical hyperplasia, adenoma, and adenocarcinoma) (Waalkes *et al.* 1995). Rats exposed to lead phosphate by subcutaneous injection (alone or followed by intraperitoneal injection) developed benign or malignant kidney tumors (adenoma or carcinoma). Rats exposed to lead chromates by subcutaneous injection developed cancer at the injection site (sarcoma), and administration of lead chromates by intramuscular injection caused kidney cancer (renal-cell carcinoma) (IARC 1990). (Because lead chromate is also a hexavalent chromium compound, it is also included in the listing for Chromium Hexavalent Compounds.) Tetraethyl lead administered by subcutaneous injection caused lymphoma in female mice. Exposure to lead naphthenate, lead carbonate, lead arsenate, lead nitrate, and metallic lead (as lead powder) did not significantly increase tumor incidences in experimental animals (IARC 1980).

Studies on Mechanisms of Carcinogenesis

Exposure of rodents to lead compounds also increased the incidence or accelerated the appearance of kidney tumors induced by other carcinogens, including *N*-ethyl-*N*-hydroxyethylnitrosamine and *N*-(4'-fluoro-4-biphenyl)acetamide. Higher incidences of kidney and liver cancer were observed in rats fed diets containing lead subacetate and 2-acetylaminofluorene than in rats fed either lead subacetate or 2-acetylaminofluorene alone (IARC 1980, 1987).

Absorption of lead is affected by age, the chemical form of the lead, and minerals in the diet (e.g., iron, calcium, and zinc) (ATSDR 1999). Gastrointestinal absorption of lead is greater in children than in adults (Hammad *et al.* 1996). Once absorbed, lead is distributed to blood plasma, the nervous system, and soft tissues. It subsequently is redistributed and accumulates in bone; 75% to 90% of the lead body burden is found in bones and teeth.

In studies of humans occupationally exposed to lead, there is evidence to suggest that lead damages chromosomes or DNA. In most studies, lead caused micronucleus formation, chromosomal aberrations, and DNA damage, but studies on sister chromatid exchange gave conflicting results. Genetic studies on humans environmentally exposed to lead also gave conflicting results. Lead did not cause mutations in bacteria, and results from test systems using mammalian cells were conflicting. Lead caused chromosomal aberrations in most studies in plants or mammals, both *in vitro* and *in vivo*. It caused DNA damage or fragmentation in mammals *in vivo* and in cell-free systems (in the presence of hydrogen peroxide), but mammalian *in vitro* studies gave conflicting results. Lead also inhibited the activity of DNA and RNA polymerase in cell-free systems and in mammalian cell cultures. Conflicting results were observed for sister chromatid exchange and micronucleus formation in mammalian test systems (*in vitro* and *in vivo*) (ATSDR 1999, NTP 2003).

The mechanisms by which lead causes cancer are not understood. Lead compounds do not appear to cause genetic damage directly, but may do so through several indirect mechanisms, including inhibition of DNA synthesis and repair, oxidative damage, and interaction with DNA-binding proteins and tumor-suppressor proteins (NTP 2003).

Properties

Elemental lead is an odorless, silver-bluish-white metal that is insoluble in water (Budavari *et al.* 1996, Lide and Frederikse 1998, HSDB 2009). It is soft, highly malleable, ductile, and a relatively poor conductor of electricity. It is resistant to corrosion but tarnishes upon exposure to air. Lead exists in the valence states of +2 and +4 and has four naturally occurring stable isotopes: ²⁰⁴Pb, ²⁰⁶Pb, ²⁰⁷Pb, and ²⁰⁸Pb. Inorganic lead compounds usually consist of lead in the divalent state (+2), and the chemistry of divalent lead is similar to that of group 2 metals (beryllium, magnesium, calcium, strontium, and barium).

Lead compounds may be divided between those compounds that are relatively soluble in water and those that are relatively insoluble in water. Compounds are considered soluble or insoluble based on the following criteria: (1) If a solubility constant (K_{sp}) is available, a compound with a value greater than or equal to the K_{sp} for lead chloride (1×10^{-4}) is considered soluble. (2) If a K_{sp} is not available, a compound is considered soluble if more than 2 g of the compound dissolves in 100 mL of water. (3) If no numeric solubility data are available, the compounds are considered soluble or insoluble according to the general rules of solubility.

The major soluble lead compounds are lead acetate, lead acetate trihydrate, lead chloride, lead nitrate, and lead subacetate; all are soluble in water, and lead acetate trihydrate is miscible with water. Lead acetate exists as colorless or white crystals, granules, or powders that are soluble in glycerol and slightly soluble in ethanol. Lead acetate trihydrate occurs as white crystals that are slightly soluble in ethanol and acetone. Lead chloride exists as a white crystalline powder that is insoluble in ethanol. Lead nitrate occurs as colorless or white crystals that are insoluble in nitric acid. Lead subacetate is a white heavy powder that is soluble in ethanol (HSDB 2009).

The major insoluble lead compounds include 17 inorganic lead compounds. Lead arsenate, lead azide, lead bromide, lead fluoride, lead phosphate, lead stearate, lead sulfate, and lead thiocyanate occur as white powders, crystals, or needles. Lead carbonate occurs as colorless rhombic crystals, and lead fluoborate occurs as a colorless crystalline powder. Lead chromate, lead iodide, lead naphthenate, lead oxide, and lead styphnate occur as yellow to reddish-yellow powder, crystals, or paste. Lead sulfide occurs as metallic black cubic crystals, and lead tetraoxide is a bright-red heavy powder. Lead arsenate, lead fluoride, and lead phosphate are soluble in nitric acid, and lead arsenate, lead carbonate, lead oxide, lead phosphate, lead sulfate, and lead thiocyanate are soluble in potassium hydroxide or other alkalis. Lead bromide, lead iodide, lead oxide, lead phosphate, and lead sulfate are insoluble in alcohol, and lead fluoborate decomposes in alcohol. Lead tetraoxide is soluble in hydrochloric and acetic acids and insoluble in ethanol. The reported melting points of these compounds range from 100°C (lead naphthenate) to 1,170°C (lead sulfate). All of the insoluble inorganic lead compounds have high boiling points (up to 1,470°C); however, lead carbonate decomposes before it boils, and lead azide explodes at 350°C. Most of these compounds have high specific gravities, ranging from 6.2 for lead sulfate to 9.53 for lead oxide, but a few have lower specific gravities, including lead naphthenate (1.15), lead fluoborate (1.75), and lead thiocyanate (3.82) (HSDB 2009, Akron 2010).

Tetraethyl lead and tetramethyl lead are insoluble organic lead compounds. They both exist as colorless liquids and are soluble in

benzene, ethanol, and diethyl ether. The octanol-water partition coefficients are 4.15 for tetraethyl lead and 2.97 for tetramethyl lead (HSDB 2009). The following table lists physical and chemical properties for lead, the major soluble inorganic lead compounds, and the organic lead compounds.

Substance	Specific gravity	Melting pt.	Boiling pt.
Lead	11.34	327°C	1,740°C
Lead acetate	3.25	280°C	dec
Lead acetate trihydrate	2.55	75°C	200°C (dec)
Lead chloride	5.85	501°C	950°C
Lead nitrate	4.53	470°C	dec
Lead subacetate	NR	75°C	dec
Tetraethyl lead	1.659	-136.8°C	200°C
Tetramethyl lead	1.995	-30.2°C	110°C

Source: HSDB 2009. dec = decomposes. NR = not reported.

Use

In worldwide metal use, lead ranks behind only iron, copper, aluminum, and zinc (Howe 1981). Its largest use is in lead-acid storage batteries for motor vehicles and general industry. Lead metal also is commonly used for ammunition, cable covering, piping, brass and bronze, bearing metals for machinery, and sheet lead (ATSDR 1999).

All of the major soluble lead compounds have industrial uses. Lead acetate is used as a water repellent, for mildew protection, and as a mordant for cotton dyes. Lead acetate trihydrate is used in varnishes, chrome pigments, and as an analytical reagent, and lead chloride is used in asbestos clutch or brake linings, as a catalyst, and as a flame retardant. Lead nitrate is used in the manufacture of matches and explosives, as a heat stabilizer in nylon, and as a coating on paper for photothermography. Lead subacetate is used in sugar analysis and for clarifying solutions of organic substances (HSDB 2009).

The insoluble lead compounds also have a variety of uses. Lead azide and lead styphnate both are used in munitions manufacture. Lead carbonate, lead fluoride, lead fluoborate, and lead naphthenate are used as catalysts, with additional uses in the electronic and optical industries (lead fluoride), in coatings for thermographic copying (lead carbonate), as a curing agent for epoxy resins (lead fluoborate), and as a varnish drier (lead naphthenate). Lead phosphate and lead stearate both are used as stabilizers in the plastics industry. Lead iodide and lead sulfate are used in photography; lead iodide is also used in thermoelectric materials, and lead sulfate with zinc in galvanic batteries. Lead oxide and lead sulfide are used in ceramics; lead oxide is also used as a vulcanizing agent in rubber and plastics, and lead sulfide as a humidity sensor in rockets. Lead chromate is used as a pigment in paints, rubber, and plastics; lead tetraoxide is used in plasters, ointments, glazes, and varnishes; and lead thiocyanate is used in the manufacture of safety matches and cartridges. Lead arsenate formerly was used as an insecticide and herbicide, but no current uses were found.

Organic lead (including tetraethyl lead and tetramethyl lead) was widely used in the United States as an anti-knock additive in motor-vehicle fuels until the U.S. Environmental Protection Agency initiated a phase-out of leaded gasoline in the early 1970s. By 1988, the total lead used in gasoline had been reduced to 1% of the 1970 level; in 1996, the use of lead in fuel for on-road motor vehicles was totally banned. Despite the legislated end to use of lead as a gasoline additive and reductions in some other uses of lead, overall U.S. lead consumption continued to grow until 1999, mainly because of increased production of lead-acid batteries (ATSDR 1999), but has since been on a general decline (USGS 2009, 2010, Guberman 2010).

Production

Lead is refined from mined ore, which occurs most frequently in the form of lead sulfide, also known as galena (Howe 1981). Mined lead ore is crushed and ground, and a lead concentrate is formed by separation of the various minerals. The lead concentrate is shipped to a primary smelter for refining. At the smelter, lead concentrates are sintered, roasted, and refined into lead metal that is 99.99% pure. However, secondary lead, produced from recycled scrap (primarily from lead acid batteries), accounts for the majority of lead produced in the United States.

In 2009, 400,000 metric tons (882 million pounds) of lead was mined in the United States, a slight decline from levels over the previous four years (USGS 2010). Primary lead production in the United States has declined steadily over the past several decades, from a high of 626,000 metric tons (1.4 billion pounds) in 1970 to 115,000 metric tons (254 million pounds) in 2009 (USGS 2009, 2010). In contrast, secondary lead production has increased steadily over the same period, from 450,000 metric tons (992 million pounds) in 1970 to 1,120,000 metric tons (2.5 billion pounds) in 2009, when it accounted for about 90% of the total refined lead produced in the United States. In 2009, five lead mines in Missouri, plus lead-producing mines in Alaska and Idaho, yielded most of the mined lead in the United States. Lead was processed at one smelter-refinery in Missouri. Of the 21 plants that produced secondary lead, 15 accounted for over 99% of secondary production (USGS 2010).

From 1980 to 1999, lead consumption in the United States rose steadily from 906,000 metric tons (2 billion pounds) to 1,760,000 metric tons (3.9 billion pounds), but consumption has since generally declined; in 2009, it was 1,420,000 metric tons (3.1 billion pounds). In 2009, lead was consumed at 76 manufacturing plants, with lead-acid battery production accounting for 88% of U.S. lead consumption. U.S. imports and exports of lead have fluctuated widely over the past several decades. Imports have ranged from a low of 85,000 metric tons (187 million pounds) in 1980 to a high of 365,000 metric tons (805 million pounds) in 2000; imports in 2009 were 275,000 metric tons (606 million pounds). Exports of refined lead metal have ranged from a low of 5,000 metric tons (11 million pounds) in 1976 to a high of 164,000 metric tons (362 million pounds) in 1980; exports in 2009 were 85,000 metric tons (187 million pounds) (USGS 2010).

Lead acetate was first produced in the United States in 1944; however, little production information was found. Three companies reported production of an undisclosed amount of lead acetate in 1977. Production volumes were estimated at over 6,810 kg (15,000 lb) in 1978 and over 2,270 kg (5,000 lb) in 1982, and U.S. imports were 113 kg (250 lb) in 1978 and 39,300 kg (87,000 lb) in 1982 (IARC 1980, HSDB 2009). Lead nitrate was first commercially produced in the United States in 1943, and imports of 480,000 kg (1.06 million pounds) were reported in 1978. Commercial production of lead subacetate was first reported in the United States in 1947; no production data were found (IARC 1980).

Lead carbonate has been produced commercially in the United States since the 1600s; in 1976, U.S. production was 1.48 million kilograms (3.3 million pounds), with imports in 1978 of 178,000 kg (392,000 lb) (IARC 1980). U.S. exports of lead carbonate in 2002 were 779,071 kg (1.7 million pounds) (USITC 2003). U.S. production of lead oxide in 1976 was 120 million kilograms (260 million pounds), with imports of 20 million kilograms (44 million pounds) (IARC 1980). U.S. imports of lead oxides in 2002 totaled 3.9 million kilograms (8.6 million pounds), and exports totaled 1.7 million kilograms (3.7 million pounds) (USITC 2003). Commercial production of lead naphthenate in the United States was first reported in 1944. Production of lead naphthenate was 8.2 million kilograms (18.1 million pounds)

in 1969, dropping to 2.2 million kilograms (4.9 million pounds) in 1977. U.S. production of lead tetraoxide in 1976 was 18 million kilograms (39.7 million pounds), with imports of 800,000 kg (1.8 million pounds) in 1976 and 1 million kilograms (2.2 million pounds) in 1979, and exports were estimated at 1 million to 15 million kilograms (2.2 million to 33 million pounds) in 1977 (IARC 1980).

Tetraethyl lead was first produced commercially in the United States in 1923. Production was 266 million kilograms (590 million pounds) in 1964, dropping to 148 million kilograms (330 million pounds) in 1977. U.S. imports of tetraethyl lead in 1978 were 17,000 kg (37,500 lb). Commercial production of tetramethyl lead in the United States began in 1960; 54 million kilograms (119 million pounds) was produced in 1977, and 13,800 kg (30,400 lb) was imported in 1974 (IARC 1980).

Exposure

The routes of environmental exposure to lead resulting in its absorption into the body are inhalation (with 30% to 50% of the inhaled dose absorbed into the bloodstream), ingestion (with 8% to 15% of the ingested dose absorbed into the bloodstream) and, to a limited extent, dermal contact. Lead is released to the environment from both natural and anthropogenic sources; however, most exposure results from anthropogenic sources (e.g., mining, smelting, industrial uses). Lead exists in various inorganic and organic forms, which affect its environmental fate, transport, and bioavailability. Regardless of the form, however, lead is not degraded and remains available for exposure. In the mid 1980s, combustion of leaded gasoline contributed about 90% of all anthropogenic lead emissions, but the percentage decreased sharply through the late 1990s as a result of the phase-out of leaded gasoline (ATSDR 1999, EPA 2003). Over 90% of the lead released from the combustion of leaded gasoline was in the form of inorganic lead halides (e.g., lead bromochloride), while less than 10% was in the form of organic lead alkyls (e.g., tetraethyl lead). Tetraalkyl lead compounds once accounted for 5% to 10% of the total particulate lead present in the atmosphere but are no longer present in significant quantities. Industrial processes, particularly lead smelters, are now the primary source of lead emissions and accounted for more than 78% of emissions in 2001 (EPA 2003).

According to EPA's Toxics Release Inventory, over 4,000 facilities released almost 22 million pounds of lead and 482 million pounds of lead compounds to the environment in 2007 (TRI 2009). Concentrations of lead in the air in the United States declined by 97% between 1976 and 1995 and by 57% between 1993 and 2002 (ATSDR 1999, EPA 2003). Ambient concentrations are highly variable but may exceed 10 $\mu\text{g}/\text{m}^3$ near industrial sources such as smelters (ATSDR 1999). A 1991 survey of lead levels in U.S. urban air found a maximum quarterly mean concentration of approximately 0.08 $\mu\text{g}/\text{m}^3$. Lead concentrations typically are lower in rural areas. In 1995, the estimated U.S. mean air lead concentration was 0.04 $\mu\text{g}/\text{m}^3$ (EPA 1996). The estimated daily average intake of lead by inhalation in 1991 was 2 μg for an adult living in a U.S. urban setting, significantly lower than estimates from the early 1980s (ATSDR 1999).

Lead concentrations in U.S. drinking water generally are below 5 $\mu\text{g}/\text{L}$. Lead also is found in food, cigarette smoke, and alcoholic beverages. Levels in food have declined since the elimination of lead-soldered food cans between 1979 and 1989 (ATSDR 1999). In 1990, the estimated daily intake of lead from consumption of food, water, and beverages was approximately 4 μg for children aged 2 years or younger, 6 to 9 μg for children aged 14 to 16, 6 to 9 μg for adults aged 25 to 30, and 2 to 8 μg for adults aged 60 to 65. For young children, the most common source of environmental lead exposure is direct ingestion of paint chips and lead-laden dust and soil released from

aging painted surfaces. These sources can contribute an additional daily intake of 5 μg for a toddler engaging in normal hand-to-mouth activity (CDC 1997, Lanphear *et al.* 1998).

The most common route of occupational exposure to lead is inhalation of lead fumes or lead-laden dusts in air and absorption of lead through the respiratory system. Lead may also be ingested and absorbed via the gastrointestinal tract (Bress and Bidanset 1991, Stauber *et al.* 1994). The National Institute for Occupational Safety and Health has estimated that more than three million Americans potentially are occupationally exposed to some form of lead (Staudinger and Roth 1998). Occupations having frequent high exposure to lead include battery-production worker, battery-recycling worker, foundry worker, lead chemical worker, lead smelter and refinery worker, leaded-glass worker, pigment worker, and radiator-repair worker. Occupations with a moderate frequency of high exposure include firing-range instructor, house renovator, lead miner, newspaper printer, plastics worker, rubber worker, and steel welder or cutter. Occupations with a low frequency of high exposure include automobile-repair worker, cable-production worker, construction worker, demolition worker, firing-range participant, flame-solder worker, plumber or pipe fitter, pottery-glaze producer, ship-repair worker, and stained-glass producer (Fu and Boffetta 1995, ATSDR 1999). For U.S. industries identified by the Occupational Safety and Health Administration as having significant airborne lead in the workplace, the mean concentration ranged from 165 $\mu\text{g}/\text{m}^3$ at secondary smelters to 200 $\mu\text{g}/\text{m}^3$ at storage-battery plants and brass, bronze, and copper foundries (Froines *et al.* 1990).

Regulations

Consumer Product Safety Commission (CPSC)

Accessible parts of products designed or intended primarily for children 12 and younger may not contain more than 300 ppm of lead; products exceeding this level are banned hazardous substances.

Paint or any other surface-coating materials for consumer use shall not contain lead at levels greater than 90 ppm.

Toys and other items for child use that bear paint with lead at levels greater than 0.06% of the total weight of the solid or dried paint film are banned.

Furniture articles for consumer use that bear paint with lead at levels greater than 0.06% of the total weight of the solid or dried paint film are banned.

Metal-cored candlewicks containing more than 0.06% lead by weight in the metal, and candles with such wicks, are banned.

Department of Transportation (DOT)

Numerous specific lead compounds, and lead compounds not otherwise specified, are considered hazardous materials and marine pollutants, and special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Clean Air Act

National Ambient Air Quality Standards: National primary and secondary ambient air quality standard = 1.5 $\mu\text{g}/\text{m}^3$ for lead and lead compounds.

National Emissions Standards for Hazardous Air Pollutants: Lead compounds are listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture of tetraethyl lead and tetramethyl lead is subject to provisions for the control of volatile organic compound emissions.

Prevention of Accidental Release: Threshold quantity (TQ) = 10,000 lb for tetramethyl lead.

Urban Air Toxics Strategy: Lead compounds are identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Mobile Source Air Toxics: Lead compounds are listed as a mobile source air toxic for which regulations are to be developed.

As defined by the Clean Air Act, gasoline which contains lead additives or contains lead at a concentration greater than 0.05 g/gal shall not be sold for use in motor vehicles.

Clean Water Act

Biosolids Rule: Limits have been established for lead in biosolids (sewage sludge) when used or disposed of via land application or incineration.

Effluent Guidelines: Lead and lead compounds are listed as toxic pollutants.

Numerous lead compounds are designated as hazardous substances.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb for lead, lead acetate, lead chloride, lead fluoroborate, lead fluoride, lead iodide, lead nitrate, lead phosphate, lead stearate, lead subacetate, lead sulfate, lead sulfide, lead thiocyanate, and tetraethyl lead; = 1 lb for lead arsenate.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Lead and lead compounds are listed substances subject to reporting requirements.

Reportable quantity (RQ) = 10 lb for tetraethyl lead; = 100 lb for tetramethyl lead.
Threshold planning quantity (TPQ) = 100 lb for tetraethyl lead and tetramethyl lead.

Federal Insecticide, Fungicide, and Rodenticide Act

All registrations for pesticides that have lead arsenate as an active ingredient have been canceled.

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxicity characteristic leaching procedure (TCLP) threshold = 5.0 mg/L.

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of lead or lead compounds = F035, F037, F038, K002, K003, K005, K046, K048, K049, K051, K052, K061, K062, K064, K069, K086, K100, K176, P110, P116, U144, U145, U146.

Lead and lead compounds are listed as hazardous constituents of waste.

Safe Drinking Water Act

Treatment technique, action level = 0.015 mg/L for lead.

Numerous requirements have been established to reduce exposure to lead in drinking water due to lead leaching from lead pipes and lead fittings.

Toxic Substances Control Act

A seller must disclose to the purchaser of a home any known lead-based paint hazards.

Comprehensive regulations have been developed to prevent lead-based paint poisoning in certain residential structures.

Food and Drug Administration (FDA)

A conspicuous label shall be on the surface of ornamental or decorative ceramics that contain lead warning that the vessel is not for food use and may be harmful if used for such.

A number of food additives generally recognized as safe are permitted for use in foods for human consumption providing maximum lead levels do not exceed concentrations prescribed in 21 CFR 84.

Action levels for lead in ceramic ware, hollowware, cups, mugs, and pitchers range from 0.5 to 7 µg/mL of leaching solution.

Lead acetate hair coloring must provide warning labels and may be safely used in cosmetics intended for coloring hair on the scalp if lead levels do not exceed 0.6% (weight to volume).

Lead solder may not be used in food packaging.

Maximum allowed levels of lead in various color additives used in food, drugs, cosmetics, and medical devices are provided 21 CFR 73 and 74.

Maximum permissible level of lead in bottled water = 0.005 mg/L.

Select food additives are permitted for use in animal feed with maximum lead levels ranging from 10 to 30 ppm.

Restrictions on the use of lead in various food additives are prescribed in 21 CFR 172.

Limits on the use of lead in feed and drinking water of animals are prescribed in 21 CFR 584.

Tin-coated lead foil capsules shall not be used for wine bottles.

Department of Housing and Urban Development (HUD)

HUD's Lead-Based Paint Disclosure Rule requires that a seller or lessor disclose to the purchaser the presence of any lead-based paint in a home for sale, provide an EPA pamphlet on the health effects of lead, provide records on lead-based paint used in home, and provide a 10-day period to conduct a home inspection for lead-based paint or lead-based paint hazards.

HUD has established regulations to implement the provisions set forth in the Residential Lead-Based Paint Hazard Reduction Act. In part, the goals of these regulations are to develop a national strategy to build the infrastructure necessary to eliminate lead-based paint hazards in all housing as expeditiously as possible, and to ensure that the existence of lead-based paint hazards is taken into account in the development of government housing policies and in the sale, rental, and renovation of homes and apartments.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 0.050 mg/m³ for metallic lead, inorganic lead compounds, and organic lead soaps.

Comprehensive standards have been developed for occupational exposure to metallic lead, all inorganic lead compounds, and organic lead soaps.

Guidelines**American Conference of Governmental Industrial Hygienists (ACGIH)**

Threshold limit value – time-weighted average (TLV-TWA) = 0.05 mg/m³ for lead, inorganic lead compounds, and lead chromate; = 0.15 mg/m³ for tetramethyl lead; = 0.1 mg/m³ for tetraethyl lead.

Consumer Product Safety Commission (CPSC)

Manufacturers are requested to eliminate the use of lead that may be accessible to children from products used in or around households, schools, or in recreation.

It is recommended that before purchasing products for resale, importers, distributors, and retailers make assurances that those products do not contain lead that may be accessible to children.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 0.05 mg/m³ (as metallic lead) for metallic lead, lead oxides, and lead salts (including organic salts such as lead soaps but excluding lead arsenate); = 0.002 mg/m³ (as arsenic) for lead arsenate (15-min exposure) (listing for inorganic arsenic compounds).

Immediately dangerous to life and health (IDLH) limit = 100 mg/m³ (as metallic lead).

Air concentrations should be maintained so that worker blood-lead levels remain at less than 0.06 mg Pb/100 g of whole blood.

References

- Akron. 2010. The Chemical Database. The Department of Chemistry at the University of Akron. <http://ull.chemistry.uakron.edu/erd> and search on CAS number. Last accessed: 3/23/10.
- ATSDR. 1999. *Toxicological Profile for Lead (Final Report)*. Agency for Toxic Substances and Disease Registry. <http://www.atsdr.cdc.gov/toxprofiles/tp13.pdf>.
- Bress WC, Bidanset JH. 1991. Percutaneous *in vivo* and *in vitro* absorption of lead. *Vet Hum Toxicol* 33(3): 212-214.
- Budavari SM, O'Neal J, Smith A, Heckelman PE, eds. 1996. *The Merck Index*, 12th ed. Whitehall, NJ: Merck & Company.
- CDC. 1997. Update: blood lead levels—United States 1991-1994. *Morbidity and Mortality Weekly Report* 46(7): 141-146.
- EPA. 1996. *National Air Quality and Emissions Trends Report, 1995*. U.S. Environmental Protection Agency. <http://www.epa.gov/airtrends/aqtrnd95/report>.
- EPA. 2003. Lead. In *Latest Findings on National Air Quality: 2002 Status and Trends*. U.S. Environmental Protection Agency. http://www.epa.gov/airtrends/aqtrnd02/2002_airtrends_final.pdf. p. 17.
- Froines JR, Baron S, Wegman DH, O'Rourke S. 1990. Characterization of the airborne concentrations of lead in U.S. industry. *Am J Ind Med* 18(1): 1-17.
- Fu H, Boffetta P. 1995. Cancer and occupational exposure to inorganic lead compounds: a meta-analysis of published data. *Occup Environ Med* 52(2): 73-81.
- Guberman DE. 2010. Lead [Advance Release]. In *Minerals Yearbook, Vol. I, Metals and Minerals*. U.S. Geological Survey. <http://minerals.usgs.gov/minerals/pubs/commodity/lead/myb1-2008-lead.pdf>.
- Hammad TA, Sexton M, Langenberg P. 1996. Relationship between blood lead and dietary iron intake in preschool children. A cross-sectional study. *Ann Epidemiol* 6(1): 30-33.
- Howe HE. 1981. Lead. In *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd ed, vol. 14. New York: John Wiley & Sons. pp. 98-139.
- HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. Last updated: 5/20/99. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number or compound name.
- IARC. 1980. Lead and lead compounds. In *Some Metals and Metallic Compounds*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 23. Lyon, France: International Agency for Research on Cancer. pp. 325-415.
- IARC. 1987. Lead and lead compounds. In *Overall Evaluations of Carcinogenicity*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, suppl 7. Lyon, France: International Agency for Research on Cancer. pp. 230-232.
- IARC. 1990. Chromium and chromium compounds. In *Chromium, Nickel, and Welding*. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 49. Lyon, France: International Agency for Research on Cancer. pp. 49-256.
- Lanphear BP, Matte TD, Rogers J, Clickner RP, Dietz B, Bornschein RL, et al. 1998. The contribution of lead-contaminated house dust and residential soil to children's blood lead levels. A pooled analysis of 12 epidemiologic studies. *Environ Res* 79(1): 51-68.
- Lide DR, Frederikse HPR, eds. 1998. *CRC Handbook of Chemistry and Physics*. New York: CRC Press.
- NTP. 2003. *Report on Carcinogens Background Document for Lead and Lead Compounds*. National Toxicology Program. <http://ntp.niehs.nih.gov/ntp/newhomero/c/roc11/Lead-Public.pdf>.
- Stauber JL, Florence TM, Gulson BL, Dale LS. 1994. Percutaneous absorption of inorganic lead compounds. *Sci Total Environ* 145(1-2): 55-70.
- Staudinger KC, Roth VS. 1998. Occupational lead poisoning. *Am Fam Physician* 57(4): 719-726, 731-732.
- Steenland K, Boffetta P. 2000. Lead and cancer in humans: where are we now? *Am J Ind Med* 38(3): 295-299.
- TRI. 2009. *TRI Explorer Chemical Report*. U.S. Environmental Protection Agency. <http://www.epa.gov/triexplorer/> and select Lead.
- USGS. 2009. Lead statistics. In *Historical Statistics for Mineral and Material Commodities in the United States*. U.S. Geological Survey. Last updated: 11/5/09. <http://minerals.usgs.gov/ds/2005/140/lead.pdf>.
- USGS. 2010. Lead. In *Mineral Commodity Summaries*. U.S. Geological Survey. <http://minerals.usgs.gov/minerals/pubs/commodity/lead/mcs-2010-lead.pdf>. 2 pp.
- USITC. 2003. *USITC Interactive Tariff and Trade DataWeb*. United States International Trade Commission. http://dataweb.usitc.gov/scripts/user_set.asp and search on HTS nos. 283670 and 282490. Last accessed: 2003.

Waalkes MP, Diwan BA, Ward JM, Devor DE, Goyer RA. 1995. Renal tubular tumors and atypical hyperplasias in B6C3F₁ mice exposed to lead acetate during gestation and lactation occur with minimal chronic nephropathy. *Cancer Res* 55(22): 5265-5271.

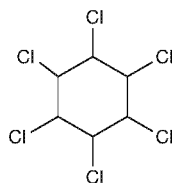
Lindane, Hexachlorocyclohexane (Technical Grade), and Other Hexachlorocyclohexane Isomers

CAS No. 58-89-9 (Lindane)

Reasonably anticipated to be human carcinogens

First listed in the *Second Annual Report on Carcinogens* (1981)

Lindane is also known as γ -hexachlorocyclohexane



Carcinogenicity

Lindane (as γ -hexachlorocyclohexane), hexachlorocyclohexane (technical grade), and other hexachlorocyclohexane isomers are *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to technical-grade hexachlorocyclohexane or individual isomers caused tumors in rodents at two different tissue sites. Dietary administration of technical-grade hexachlorocyclohexane (66.5% α isomer, 11.4% β isomer, 15.2% lindane, 6.4% δ isomer, and 0.5% other isomers), lindane, α - or β -hexachlorocyclohexane, or mixtures of various isomers caused liver tumors in both sexes of several strains of mice (IARC 1979). Dietary administration of the α isomer also caused liver tumors in rats (Schulte-Hermann *et al.* 1981, IARC 1987). In addition, dietary exposure to technical-grade hexachlorocyclohexane caused tumors of the lymphoreticular system in mice of both sexes (Kashyap *et al.* 1979, IARC 1982).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to hexachlorocyclohexane or its isomers. Three cases of leukemia (paramyeloblastic and myelomonocytic) were reported in men exposed to lindane with or without coexposure to other chemicals (IARC 1974, 1979). Many cases of aplastic anemia have also been associated with exposure to hexachlorocyclohexane or lindane, and death from lung cancer was increased among agricultural workers who had used hexachlorocyclohexane (unspecified) and a variety of other pesticides and herbicides.

Properties

Hexachlorocyclohexane isomers, including lindane, are organochlorine pesticide compounds that are brownish to white crystalline powders with a penetrating musty odor (IARC 1974). Technical-grade hexachlorocyclohexane is a mixture of several hexachlorocyclohexane isomers. Each isomer has slightly different physical and chemical properties, including solubilities. The α isomer is practically insoluble in water but soluble in chloroform and benzene. The β isomer is very slightly soluble in water and slightly soluble in chloroform and benzene. The γ isomer (lindane) is practically insoluble in water but

very soluble in chloroform, ethanol, acetone, ether, and benzene. The δ isomer is practically insoluble in water but soluble in ethanol, ether, and benzene. Technical-grade lindane (99% γ isomer) (HSDB 2009) is stable under normal temperature and pressure (Akron 2009). Physical and chemical properties of α -, β -, γ -, and δ -hexachlorocyclohexane (HCH) are listed in the following table.

Property	α -HCH	β -HCH	γ -HCH	δ -HCH
Molecular weight	290.8	290.8	290.8	290.8
Specific gravity	1.87	1.89	1.85	NA
Melting point	158°C	309°C	112.5°C	141.5°C
Boiling point	288°C	60°C at 0.50 mm Hg	323.4°C at 760 mm Hg	60°C at 0.36 mm Hg
Log K_{ow}	3.8	3.78	3.72	4.14
Water solubility	0.002 g/L ^a	0.0002 g/L ^b	0.0073 g/L ^a	0.0314 g/L ^a
Vapor pressure	4.5×10^{-5} mm Hg ^a	3.6×10^{-7} mm Hg ^b	4.20×10^{-5} mm Hg ^b	3.5×10^{-5} mm Hg ^a

Source: HSDB 2009. NA = not available. ^aAt 25°C. ^bAt 20°C

Use

The only identified uses for hexachlorocyclohexane-containing products are based on the insecticidal activity of the γ isomer (lindane), which is considered to be the only insecticidally effective component (Exttoxnet 1996). Lindane or technical-grade hexachlorocyclohexane containing the γ isomer is used primarily as an insecticide in the treatment of wood and wooden structures, seed grains, and livestock (ATSDR 2005, HSDB 2009). Other major uses are as an insecticide for several dozen fruit and vegetable crops, in baits and seed treatments for rodent control, and for treatment of scabies (mites) and lice. It is approved by the U.S. Food and Drug Administration for use in three products for the treatment of lice and scabies (one lotion and two shampoos) (FDA 2009). Agricultural and pesticide uses accounted for about 270,000 kg (594,000 lb) of lindane and 450,000 kg (1 million pounds) of technical-grade hexachlorocyclohexane in 1974; the remaining uses were industrial or pharmaceutical (IARC 1979).

Production

Technical-grade hexachlorocyclohexane is produced as a mixture of isomers (primarily the α , β , γ , δ , and ϵ isomers) by photochlorination of benzene, a reaction that can be started by free-radical initiators such as visible or ultraviolet light, X-rays, or gamma rays (ATSDR 2005). The active γ -hexachlorocyclohexane (lindane) can be concentrated by treatment with methanol or acetic acid, followed by fractional crystallization, which produces technical grade lindane containing 99.9% γ isomer. Commercial production of lindane in the United States began in 1945 and peaked in the 1950s, when 17.6 million pounds was manufactured (IARC 1974). Lindane is no longer produced commercially in the United States, but it is produced by 13 manufacturers worldwide, including 7 in India and 4 in China (SRI 2009), and is available from 42 suppliers, including 19 U.S. suppliers (ChemSources 2009). U.S. imports of hexachlorocyclohexane increased from 310,000 lb to 1.4 million pounds between 1989 and 1999 imports, declining to zero in 2005 and remaining zero through 2008 except in 2006, when 73,000 lb was imported. U.S. exports of hexachlorocyclohexane increased from zero in 1990 to 1.5 million pounds in 2005, declining to 154,000 lb in 2008 (USITC 2009).

Exposure

The routes of potential human exposure to lindane and other hexachlorocyclohexane isomers are ingestion, inhalation, and dermal contact (HSDB 2009). The general population potentially is exposed through consumption of foodstuffs contaminated with pesticide residues. According to U.S. Food and Drug Administration's Total Diet

Survey, lindane was detected in 279 of 2,168 samples and in at least one sample of all 54 different food items analyzed (FDA 2006). Most of the food items in which lindane was detected had significant fat content; however, the highest lindane concentrations were in pickles and raw mushrooms, which have low fat content. Daily dietary intake of hexachlorocyclohexane isomers by the adult U.S. population was estimated at 0.010 µg/kg (10 ng/kg) of body weight for all isomers and 0.002 µg/kg (2 ng/kg) for lindane. For 1982 to 1984, the estimated dietary intake of lindane was 1.9 ng/kg of body weight for infants aged 6 to 11 months and 7.9 ng/kg for toddlers aged two years, who had the highest average daily intake. By 1986 to 1991, daily intake had fallen to 0.8 ng/kg for infants and 3.2 ng/kg for toddlers (ATSDR 2005).

Dermal exposure occurs when shampoos and lotions containing lindane are used for the treatment of lice and scabies (FDA 2009). The highest average blood concentration of lindane measured in children after scabies treatment with one of these products was 0.028 µg/mL (ATSDR 2005).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, environmental releases of lindane ranged from 314 and 2,118 lb between 1988 and 1997. In 1998, over 25,000 lb was sent to a hazardous-waste landfill. By 2006, releases had declined to 10 lb. In 2007, five facilities released a total of 1,555 lb of lindane, mostly off site for unspecified management (TRI 2009). Lindane was found in at least 189 hazardous-waste sites currently or formerly on the National Priorities List; it occurred in air at 9 sites, surface water at 33 sites, sediment at 36 sites, and soil at 90 sites. The Non-Occupational Pesticide Exposure Study, published in 1990, collected personal air samples at one U.S. location with high pesticide usage and one with low to medium usage. The range of mean γ-hexachlorocyclohexane concentration was 7 to 22 ng/m³ at the high-usage site and 0.7 to 5 ng/m³ at the low- to medium-usage site (ATSDR 2005).

Hexachlorocyclohexane isomers have been detected in human fatty tissue, blood, and breast milk. The National Human Adipose Tissue Survey (NHATS), conducted in 1982, found β-hexachlorocyclohexane in 87% of composite post-mortem samples of fatty tissue. According to NHATS data, the mean concentration of β-hexachlorocyclohexane in fat decreased from 0.45 ppm in 1970 to 0.16 ppm in 1981. The levels were highest in the southern United States. In the 1970s, the National Health and Nutrition Examination Survey (NHANES) found β-hexachlorocyclohexane in blood at a median concentration of 1.7 ppb. When the NHANES was repeated in 1999 to 2000, the geometric mean concentration of β-hexachlorocyclohexane and γ-hexachlorocyclohexane in serum lipid was 9.68 ng/g (ppb) for individuals over 12 years of age (ATSDR 2005). β-Hexachlorocyclohexane was measured in breast milk at a concentration of 0.6 ng/g in Canadian populations living near the Great Lakes. In the Netherlands, concentrations of γ-hexachlorocyclohexane in breast-milk fat in 1988 ranged from 0.01 to 0.24 mg/kg (HSDB 2009). Many other studies in populations throughout the world, especially Arctic populations, have found hexachlorocyclohexane isomers in blood, fat, and breast-milk samples. Hexachlorocyclohexane isomers have been measured at higher concentrations in all types of samples in areas of the world where lindane is still extensively used for pest control, such as India and Africa.

The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 15,036 workers, including 5,153 women, potentially were exposed to lindane (NIOSH 1990). No occupational exposure data were found for other hexachlorocyclohexane isomers.

Regulations

Department of Transportation (DOT)

Lindane is considered a marine pollutant, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Lindane (all isomers) is listed as a hazardous air pollutant.

Clean Water Act

Effluent Guidelines: Hexachlorocyclohexane is listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.98 µg/L for lindane; = 0.0026 µg/L for the α isomer; = 0.0091 µg/L for the β isomer; based on fish or shellfish consumption only = 1.8 µg/L for lindane; = 0.0049 µg/L for the α isomer; = 0.017 µg/L for the β isomer.

Lindane is designated a hazardous substance.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb for lindane, all isomers.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Lindane and α-hexachlorocyclohexane are listed substances subject to reporting requirements.

Reportable quantity (RQ) = 1 lb for lindane.

Threshold planning quantity (TPQ) = 1,000 lb for lindane solid in powder form with particle size < 100 µm or solution or molten form; = 10,000 lb for lindane in all other forms.

Federal Insecticide, Fungicide, and Rodenticide Act

Tolerances for lindane residue in various animal fats range from 4 to 7 ppm.

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxicity characteristic leaching procedure (TCLP) threshold = 0.4 mg/L for lindane.

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of lindane or hexachlorocyclohexane = U129, F024.

Lindane is listed as a hazardous constituent of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.0002 mg/L for lindane.

Food and Drug Administration (FDA)

Maximum permissible level in bottled water = 0.0002 mg/L for lindane.

Action levels for lindane in food and in animal feed range from 0.1 to 0.5 ppm.

Lindane is a prescription drug subject to labeling and other requirements.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 0.5 mg/m³ for lindane.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.5 mg/m³ for lindane.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 0.5 mg/m³ for lindane.

Immediately dangerous to life and health (IDLH) limit = 50 mg/m³ for lindane.

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

References

- Akron. 2009. *The Chemical Database*. The Department of Chemistry at the University of Akron. <http://uakron.edu/chem> and search on CAS number. Last accessed: 12/18/09.
- ATSDR. 2005. *Toxicological Profile for Alpha-, Beta-, Gamma-, and Delta-Hexachlorocyclohexane*. Agency for Toxic Substances and Disease Registry. <http://www.atsdr.cdc.gov/toxprofiles/tp43.html>.
- ChemSources. 2009. *Chem Sources - Chemical Search*. Chemical Sources International. <http://www.chemsources.com/chemonline.html> and search on lindane. Last accessed: 12/18/09.
- Exttoxnet. 1996. *Lindane*. Extension Toxicology Network Pesticide Information Profiles. <http://exttoxnet.orst.edu/pips/lindane.htm>.
- FDA. 2006. *Total Diet Study Market Baskets 1991-3 through 2003-4*. U.S. Food and Drug Administration. <http://www.fda.gov/downloads/Food/FoodSafety/FoodContaminantsAdulteration/TotalDietStudy/UCM184304.pdf>.

FDA. 2009. *The Electronic Orange Book*. U.S. Food and Drug Administration. <http://www.fda.gov/cder/ob/default.htm> and select Search by Active Ingredient and search on lindane. Last accessed: 12/09.

HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number. Last accessed: 12/18/09.

IARC. 1974. BHC (technical grades) and lindane. In *Some Organochlorine Pesticides*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 5. Lyon, France: International Agency for Research on Cancer. pp. 47-74.

IARC. 1979. Hexachlorocyclohexane (technical HCH and lindane). In *Some Halogenated Hydrocarbons*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 20. Lyon, France: International Agency for Research on Cancer. pp. 195-239.

IARC. 1982. Hexachlorocyclohexane. In *Chemicals, Industrial Processes and Industries Associated with Cancer in Humans*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, suppl. 4. Lyon, France: International Agency for Research on Cancer. pp. 133-135.

IARC. 1987. Hexachlorocyclohexanes. In *Overall Evaluations of Carcinogenicity*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, suppl. 7. Lyon, France: International Agency for Research on Cancer. pp. 220-222.

Kashyap SK, Nigam SK, Gupta RC, Karnik AB, Chatterjee SK. 1979. Carcinogenicity of hexachlorocyclohexane (BHC) in pure inbred Swiss mice. *J Environ Sci Health B* 14(3): 305-318.

NIOSH. 1990. *National Occupational Exposure Survey (1981-83)*. National Institute for Occupational Safety and Health. Last updated: 7/1/90. <http://www.cdc.gov/noes/noes1/09318sic.html>.

Schulte-Hermann R, Parzefall W. 1981. Failure to discriminate initiation from promotion of liver tumors in a long-term study with the phenobarbital-type inducer alpha-hexachlorocyclohexane and the role of sustained stimulation of hepatic growth and monooxygenases. *Cancer Res* 41(10): 4140-4146.

SRI. 2009. *Directory of Chemical Producers*. Menlo Park, CA: SRI Consulting. Database edition. Last accessed: 5/09.

TRI. 2009. *TRI Explorer Chemical Report*. U.S. Environmental Protection Agency. Last updated: 3/19/09. <http://www.epa.gov/triexplorer> and select Lindane.

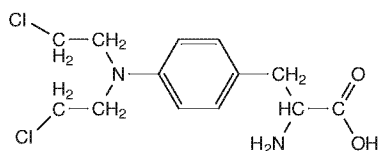
USITC. 2009. *USITC Interactive Tariff and Trade DataWeb*. United States International Trade Commission. http://datweb.usitc.gov/scripts/user_set.asp and search on HTS no. 290351. Last accessed: 3/25/09.

Melphalan

CAS No. 148-82-3

Known to be a human carcinogen

First listed in the *First Annual Report on Carcinogens* (1980)



Carcinogenicity

Melphalan is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Epidemiological studies found that patients treated with melphalan for breast cancer, ovarian cancer, and bone-marrow cancer (multiple myeloma) had an increased risk of leukemia (relative risk > 100). The risk of leukemia increased with increasing dose of melphalan but was not affected by co-exposure to radiation therapy (IARC 1987).

Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of melphalan from studies in experimental animals. When administered by intraperitoneal injection, melphalan caused cancer of lymphatic tissue (lymphosarcoma) in male mice, lung tumors in mice of both sexes, and cancer of the abdominal cavity (sarcoma of the peritoneum) in rats of both sexes (IARC 1975, 1987).

Properties

Melphalan is an alkylating agent that is a white to buff odorless powder at room temperature. It is practically insoluble in water, insoluble

in chloroform and ether, slightly soluble in methanol, and soluble in ethanol, propylene glycol, 2% carboxymethylcellulose, and alkaline and dilute acid solutions. It hydrolyzes in aqueous solution (IARC 1975). Physical and chemical properties of melphalan are listed in the following table.

Property	Information
Molecular weight	305.2 ^a
Melting point	182°C to 183°C (decomposes) ^a
Log <i>K</i> _{ow}	-0.52 (at pH 7) ^a
Water solubility	0.0457 g/L at 25°C ^b
Vapor pressure	3 × 10 ⁻¹⁰ mm Hg at 25°C ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Melphalan is used as a drug to treat cancer and other medical conditions, including ovarian cancer, malignant melanoma, multiple myeloma (bone-marrow cancer), breast cancer, advanced prostate cancer, testicular cancer (seminoma), chronic myelogenous leukemia, osteogenic sarcoma (childhood bone cancer), polycythemia vera (overproliferation of blood cells), amyloidosis (accumulation of amyloid protein in tissues), and scleromyxedema (a rare skin disease). It is also used as an insect chemosterilant (IARC 1975, HSDB 2009, MedlinePlus 2009).

Production

In 2009, melphalan was produced by one U.S. manufacturer (HSDB 2009) and was available from 11 U.S. suppliers (ChemSources 2009), and drug products approved by the U.S. Food and Drug Administration containing melphalan as the active ingredient were produced by one U.S. pharmaceutical company (FDA 2009). Imports of melphalan totaled 165 kg (364 lb) in 1983 (HSDB 2009). No other data on U.S. imports or exports of melphalan were found.

Exposure

The general population is not expected to be exposed to melphalan, because its use is limited to medical treatment. Melphalan is available in 2-mg tablets and in an injectable form (melphalan hydrochloride, in 50-mg vials) (FDA 2009). The usual oral dose is 6 mg daily for two to three weeks, followed by a rest period of about four weeks. Maintenance therapy is usually 2 to 4 mg per day. For intravenous therapy, the usual dose is 16 mg/m² infused over 15 to 20 minutes, repeated at two-week intervals for four doses and then at four-week intervals (Chabner *et al.* 2001). In 2009, 428 clinical trials involving melphalan were in progress or recently completed (ClinicalTrials 2009).

Health professionals who handle melphalan, such as pharmacists, nurses, and physicians, could potentially be exposed during drug preparation, administration, or cleanup; however, exposure can be avoided through use of appropriate containment equipment and work practices (Zimmerman *et al.* 1981). One study reported that exposure of hospital personnel to melphalan could be reduced by treating excess solutions, spills, and urinals with chlorine bleach (Hansel *et al.* 1997). Occupational exposure also may occur during drug formulation or packaging. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 2,418 workers, including 974 women, potentially were exposed to melphalan (NIOSH 1990).

Regulations

Consumer Product Safety Commission (CPSC)

Any orally administered prescription drug for human use requires child-resistant packaging.

Environmental Protection Agency (EPA)

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of melphalan = U150.

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

Melphalan is a prescription drug subject to specific labeling requirements.

Guidelines**National Institute for Occupational Safety and Health (NIOSH)**

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

References

- Chabner BA, Ryan DP, Paz-Ares L, Garcia-Carbonero R, Calabresi P. 2001. Antineoplastic agents. In *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 10th ed. Hardman JG, Limbird LE, eds. New York: McGraw Hill. pp. 1389-1459.
- ChemIDplus. 2009. *ChemIDplus Advanced*. National Library of Medicine. <http://chem.sis.nlm.nih.gov/chemidplus/chemidheavy.jsp> and select Registry Number and search on CAS number. Last accessed: 10/22/09.
- ChemSources. 2009. *Chem Sources - Chemical Search*. Chemical Sources International. <http://www.chemsources.com/chemonline.html> and search on melphalan. Last accessed: 10/22/09.
- ClinicalTrials. 2009. Melphalan. *ClinTrials.gov*. U.S. National Institutes of Health. <http://clinicaltrials.gov/ct2/results?term=melphalan>. Last accessed 11/19/09.
- FDA. 2009. *The Electronic Orange Book*. U.S. Food and Drug Administration. <http://www.fda.gov/cder/ob/default.htm> and select Search by Active Ingredient and search on melphalan. Last accessed: 10/22/09.
- Hansel S, Castegnaro M, Sportouch MH, De Meo M, Milhavet JC, Laget M, Dumenil G. 1997. Chemical degradation of wastes of antineoplastic agents: cyclophosphamide, ifosfamide and melphalan. *Int Arch Occup Environ Health* 69(2): 109-114.
- HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number. Last accessed: 10/22/09.
- IARC. 1975. Melphalan, medphalan and merphalan. In *Some Aziridines, N-, S-, and O-Mustards and Selenium*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 9. Lyon, France: International Agency for Research on Cancer. pp. 167-180.
- IARC. 1987. Melphalan. In *Overall Evaluations of Carcinogenicity*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, suppl. 7. Lyon, France: International Agency for Research on Cancer. pp. 239-240.
- MedlinePlus. 2009. *Melphalan*. National Library of Medicine. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682220.html>. Last accessed: 11/19/09.
- NIOSH. 1990. *National Occupational Exposure Survey (1981-83)*. National Institute for Occupational Safety and Health. Last updated: 7/1/90. <http://www.cdc.gov/noes/noes1/x4742sic.html>.
- Zimmerman PF, Larsen RK, Barkley EW, Gallelli JF. 1981. Recommendations for the safe handling of injectable antineoplastic drug products. *Am J Hosp Pharm* 38(11): 1693-1695.

Methoxsalen with Ultraviolet A Therapy

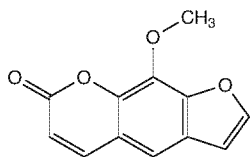
CAS No.: none assigned

Known to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)

Methoxsalen is also known as 8-methoxypsoralen (CAS No. 298-81-7)

Methoxsalen with ultraviolet A therapy is also known as PUVA

**Carcinogenicity**

Methoxsalen (psoralen) with ultraviolet A (UVA) long-wave therapy (PUVA) is known to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

A cohort study of 1,380 psoriasis patients treated with PUVA found that the risk of skin cancer (squamous-cell carcinoma) increased with increasing exposure to PUVA; exposure to high doses of PUVA increased the risk of cancer by more than 50-fold. The risk was independent of any possible confounding by treatment with ionizing radiation or coal tar. An association between basal-cell carcinoma and PUVA exposure also was observed; however, the estimated risk at high exposure was fourfold lower than that observed for squamous-cell carcinoma. Increased risks of skin cancer were not reported in two smaller cohort studies; one study included only 94 patients, and the other used a low dose and may not have had sufficient statistical power to detect an effect. A case-control study also reported an increased risk of skin cancer among psoriasis patients treated with PUVA. Supporting the association between skin cancer and PUVA exposure are several case reports of skin cancer (basal-cell and squamous-cell carcinoma and malignant melanoma) in patients treated with PUVA for psoriasis or mycosis fungoides (a form of lymphoma primarily affecting the skin). In two small randomized clinical trials evaluating whether methoxsalen would protect against sunlight-induced skin cancer (by increasing pigmentation and cornification of the skin), methoxsalen administered alone for over two years did not affect the incidence of skin cancer (IARC 1980, 1982, 1987).

Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of PUVA from studies in experimental animals. Methoxsalen administered in the diet, by intraperitoneal injection, or by dermal application in combination with ultraviolet light caused benign and malignant epidermal and dermal skin tumors in mice. These included epidermal papilloma and carcinoma, squamous-cell carcinoma, fibrosarcoma, lymphosarcoma, basal-cell carcinoma, and hemangioma. Some squamous-cell and basal-cell carcinomas metastasized. Malignant tumors of the ears and the eye region (epidermal fibrosarcoma and squamous-cell carcinoma) were observed in female mice following intraperitoneal administration of methoxsalen and exposure to ultraviolet light (IARC 1980, 1987).

Studies on Mechanisms of Carcinogenesis

Methoxsalen readily absorbs ultraviolet light, particularly UVA wavelengths (320 to 400 nm). As a photosensitizing agent, it can produce phototoxic erythema (a reaction similar to sunburn) when skin to which it has been applied receives excess exposure to UVA. Chronic reactions may result in hyperpigmentation and skin thickening. UVA causes a photochemical reaction that results formation of adducts between methoxsalen and the pyrimidine bases of DNA (Rice and Cohen 1996).

Properties

Methoxsalen belongs to a group of drugs known as psoralen derivatives and exists as white to cream-colored fluffy crystals at room temperature (NTP 1989). It is practically insoluble in water, sparingly soluble in ether and liquid petrolatum, soluble in boiling alcohol, acetone, benzene, acetic acid, fixed vegetable oils, and propylene glycol, and freely soluble in chloroform. Methoxsalen is easily hydrolyzed and is unstable in the presence of air and light (Akron 2009). Physical and chemical properties of methoxsalen are listed in the following table. (For properties of ultraviolet radiation, see the profile for Ultraviolet Radiation Related Exposures.)

Property	Information
Molecular weight	216.2 ^a
Density	1.539 g/cm ^{3b}
Melting point	148°C ^a
Boiling point	415°C ^b
Log <i>K</i> _{ow}	2.14 ^c
Water solubility	0.0476 g/L at 30°C ^c
Vapor pressure	4 × 10 ⁻⁷ mm Hg at 25°C ^b

Sources: ^aHSDB 2009, ^bAkron 2009, ^cChemIDplus 2009.

Use

Psoralen-containing plant extracts were first used in photochemotherapy to treat vitiligo in Egypt and India as far back as 1500 B.C. The acronym PUVA was coined in 1974 following successful treatment of severe psoriasis with 8-methoxypsoralen and UVA. Methoxsalen is now used in combination with UVA in the treatment of vitiligo, severe psoriasis, atopic dermatitis, alopecia areata, lichen planus, urticaria pigmentosa, cutaneous T-cell lymphoma, and some forms of photosensitivity (Wyatt *et al.* 2001).

Topical, bath, oral, and extracorporeal (outside the body) treatments are available by prescription only. To treat vitiligo, the topical solution is applied to the affected area and allowed to dry for several minutes before a second application, and the treated area is exposed to UVA about 2 hours later. For bath treatment of small areas (e.g., hands and feet), the area to be treated is soaked in a dilute solution of methoxsalen for 30 minutes and then immediately exposed to UVA. Oral preparations include hard and soft gelatin capsules for treatment of mycosis fungoides, psoriasis, and vitiligo; they may be given two or three times per week with at least 48 hours between doses. Methoxsalen also is used along with UVA to treat white blood cells to control skin problems caused by cutaneous T-cell lymphoma, a cancer of the lymphatic system. The white blood cells are removed from the blood, treated in a process called “photopheresis,” and returned to the body (LLS 2006).

Production

Methoxsalen is produced naturally by several plants (e.g., limes, celery, figs, and parsnips) found in both temperate and tropical regions (Drugge and Dunn 2003). It was first marketed in the United States in 1955. In 1980, one U.S. company reportedly produced the chemical, but no production data were available (IARC 1980). In 2009, no U.S. producers of methoxsalen were identified (SRI 2009), but it was available from 14 U.S. suppliers (ChemSources 2009), and four drug products approved by the U.S. Food and Drug Administration containing methoxsalen as the active ingredient were produced by two U.S. pharmaceutical companies (FDA 2009).

Exposure

The primary routes of human exposure to methoxsalen are dermal contact and ingestion. Individuals with skin diseases may be exposed to PUVA during treatment. Methoxsalen rapidly penetrates the epidermis and dermis upon contact with the skin. For medicinal effectiveness, both oral and topical administration require subsequent exposure to UVA (at 320 to 400 nm). Methoxsalen formulations are available in 10-mg capsules (hard and soft), 1% topical solutions, and 0.02 mg/mL injectable solutions (FDA 2009). The oral dosage (for adults and children aged 12 years or older) is 0.4 to 0.6 mg/kg of body weight, given 1.5 to 4 hours before UVA exposure (Wyatt *et al.* 2001). Because of differences in phototoxic response, the initial UVA dose must be determined for each individual. Under one protocol, the initial UVA dose is based on an individual's minimal phototoxic dose (the dose that when given with the appropriate dose of methox-

salen produces erythema), which is determined by exposing small areas of the thigh to UVA doses increasing from 0.5 to 9 J/cm². Alternatively, the initial UVA dose is based on the patient's skin type; patients with fairer skin that burns easily receive lower doses than those with darker skin that is less prone to burn. Following the initial dose, therapy usually is repeated two to four times per week, and the UVA dose is increased by 0.5 to 2.0 J/cm² per treatment. Generally, the dose of methoxsalen is not increased during treatment (Kostović *et al.* 2002). No information was found regarding the number of people treated with PUVA therapy.

Occupational exposure to methoxsalen may occur during preparation, formulation, administration, or application of the pharmaceutical products. Individuals occupationally exposed to methoxsalen may also be exposed to ultraviolet light during therapy or during subsequent exposure to sunlight.

Regulations

Consumer Product Safety Commission (CPSC)

Any orally administered prescription drug for human use requires child-resistant packaging.

Food and Drug Administration (FDA)

PUVA is regulated as a prescription drug or therapy.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

References

- Akron. 2009. *The Chemical Database*. The Department of Chemistry at the University of Akron. <http://ull.chemistry.uakron.edu/erd> and search on CAS number. Last accessed: 7/7/09.
- ChemIDplus. 2009. *ChemIDplus Advanced*. National Library of Medicine. <http://chem.sis.nlm.nih.gov/chemidplus/chemidheavy.jsp> and select Registry Number and search on CAS number. Last accessed: 10/22/09.
- ChemSources. 2009. *Chem Sources - Chemical Search*. Chemical Sources International. <http://www.chemsources.com/chemonline.html> and search on methoxsalen. Last accessed: 10/22/09.
- Drugge R, Dunn HA, eds. 2004. Botanical dermatology: phytophotodermatitis. In *The Electronic Textbook of Dermatology*. Internet Dermatology Society. <http://www.telemedicine.org/botanica/bot5.htm>. Last accessed: 2/21/04.
- FDA. 2009. *The Electronic Orange Book*. U.S. Food and Drug Administration. <http://www.fda.gov/cder/ob/default.htm> and select Search by Active Ingredient and search on methoxsalen. Last accessed: 10/22/09.
- HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number. Last accessed: 10/22/09.
- IARC. 1980. Methoxsalen. In *Some Pharmaceutical Drugs*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 24. Lyon, France: International Agency for Research on Cancer. pp. 101-124.
- IARC. 1982. Methoxsalen with ultra-violet A therapy (PUVA). In *Chemicals, Industrial Processes and Industries Associated with Cancer in Humans*, IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, suppl. 4, Lyon, France: International Agency for Research on Cancer. pp. 158-160.
- IARC. 1987. 8-Methoxypsoralen (methoxsalen) plus ultraviolet radiation (Group 1). In *Overall Evaluations of Carcinogenicity*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, suppl 7. Lyon, France: International Agency for Research on Cancer. pp. 243-245.
- Kostović K, Šitum M, Nola I. 2002. Phototherapy (UVB) and photochemotherapy (PUVA) for psoriasis. *Acta Clin Croat* 41: 103-112.
- LLS. 2006. *Cutaneous T-Cell Lymphoma*. The Leukemia & Lymphoma Society. http://www.leukemia-lymphoma.org/attachments/National/br_1163608564.pdf.
- NTP. 1989. *Toxicology and Carcinogenesis Studies of 8-Methoxypsoralen (CAS No. 298-81-7) in F344/N Rats (Gavage Studies)*. Technical Report Series no. 359. Research Triangle Park, NC: National Toxicology Program. 134 pp.
- Rice RH, Cohen DE. 1996. Toxic responses of the skin. In *Casarett and Doull's Toxicology, the Basic Science of Poisons*, 5th ed. Klaassen CD, Amdur MO, Doull J, eds. New York: McGraw-Hill. pp. 529-546.
- SRI. 2009. *Directory of Chemical Producers*. Menlo Park, CA: SRI Consulting. Database edition. Last accessed: 10/22/09.

Wyatt EL, Sutter SH, Drake LA. 2001. Dermatological pharmacology. In *Goodman and Gillman's The Pharmacological Basis of Therapeutics*. Hardman JG, Limbird LE, eds. New York: McGraw Hill. pp. 1795-1818.

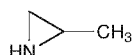
2-Methylaziridine

CAS No. 75-55-8

Reasonably anticipated to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)

Also known as propylenimine



Carcinogenicity

2-Methylaziridine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to 2-methylaziridine caused tumors at several different tissue sites in rats. Administration of 2-methylaziridine by stomach tube for 28 or 60 weeks caused mainly mammary-gland cancer in females and leukemia in males. Increased incidences were also reported for cancer of the central nervous system (glioma) and ear canal (squamous-cell carcinoma) in both sexes and of the intestine (adenocarcinoma) in males (IARC 1975, 1999, Weisburger *et al.* 1981).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to 2-methylaziridine.

Properties

2-Methylaziridine is the simplest heterocyclic amine and is a reactive alkylating agent (IARC 1999). It exists at room temperature as a colorless oily liquid with an ammonia-like odor and is miscible with water and soluble in ethanol and most organic solvents (Akron 2009, HSDB 2009). 2-Methylaziridine undergoes violent polymerization on contact with acids or acid vapors and may explode. Physical and chemical properties of 2-methylaziridine are listed in the following table.

Property	Information
Molecular weight	57.1 ^a
Specific gravity	0.812 at 16°C/4°C ^a
Melting point	-65°C ^a
Boiling point	66°C to 67°C at 760 mm Hg ^a
Log <i>K</i> _{ow}	0.13 ^b
Water solubility	1,000 g/L ^b
Vapor pressure	112 mm Hg at 20°C ^b
Vapor density relative to air	2 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

2-Methylaziridine is used in the United States exclusively as a chemical intermediate, and its derivatives are used in the paper, textile, rubber, and pharmaceutical industries (IARC 1975, HSDB 2009). Because it easily forms imines, its primary use is in the modification of latex surface-coating resins to improve adhesion. Because of the substantive bonding of imines to cellulose derivatives, polymers modified with 2-methylaziridine or its derivatives have been used in the adhesive, textile, and paper industries. 2-Methylaziridine has been used to modify dyes for specific adhesion to cellulose, and derivatives have been used in photography, gelatins, and synthetic resins. In the

oil-additive industry, 2-methylaziridine and its derivatives have been used as modifiers for viscosity control, high-pressure performance, and oxidation resistance. Other applications include use in flocculants in petroleum refining, as a modifier for rocket propellant fuels, in fiber modification, and in imine derivatives for use in medicinal and agricultural chemicals.

Production

In 2009, 2 methylaziridine was produced by one manufacturer in the United States and one in Europe (SRI 2009) and was available from nine suppliers, including six U.S. suppliers (ChemSources 2009). U.S. production of 2 methylaziridine was at least 100,000 lb in 1977, but had fallen to 5,000 lb by 1982 (HSDB 2009). Reports filed from 1986 through 2002 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of 2 methylaziridine totaled 10,000 to 500,000 lb (EPA 2004). No other data on U.S. production, imports, or exports of 2 methylaziridine were found.

Exposure

The primary routes of potential human exposure to 2-methylaziridine are inhalation, ingestion, and dermal contact (HSDB 2009). According to EPA's Toxics Release Inventory, environmental releases of 2-methylaziridine between 1988 and 2009 ranged from a low of 89 lb in 2000 to a high of 1,482 lb in 2009. Nearly all of the releases have been to air, with small quantities (~5 lb per year) released to surface water or off-site landfills. In 2007, three facilities released a total of 1,482 lb (TRI 2009). If released to air, 2-methylaziridine is expected to exist in the vapor phase and can react with photochemically generated hydroxyl radicals, with a half-life of 1.6 days (HSDB 2009). If released to surface water or moist soil, it is expected to hydrolyze, with a half-life of 17.5 days. Although it can be mobile in soil, 2-methylaziridine does not leach into groundwater, because it degrades very rapidly. It may also volatilize relatively slowly from wet soil or surface water but relatively rapidly from dry soil.

Because of its volatility, occupational exposure could occur during production, packaging, or use of substances made with 2-methylaziridine (HSDB 2009). The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 20 workers potentially were exposed to 2-methylaziridine in 1974 (HSDB 2009). The American Conference of Governmental Industrial Hygienists noted the potential for dermal exposure, including via the mucous membranes and eyes, by airborne or direct contact and have given 2-methylaziridine a skin designation (ACGIH 2009).

Regulations

Department of Transportation (DOT)

2-Methylaziridine is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.
Prevention of Accidental Release: Threshold quantity (TQ) = 10,000 lb.

Comprehensive Environmental Response, Compensation, and Liability Act
Reportable quantity (RQ) = 1 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.
Reportable quantity (RQ) = 1 lb.
Threshold planning quantity (TPQ) = 10,000 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of 2-methylaziridine = P067.
Listed as a hazardous constituent of waste.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 2 ppm (5 mg/m³).

Guidelines**American Conference of Governmental Industrial Hygienists (ACGIH)**

Threshold limit value – time-weighted average (TLV-TWA) = 0.2 ppm (0.5 mg/m³)
Threshold limit value – short-term exposure limit (TLV-STEL) = 0.4 ppm (1 mg/m³)

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 2 ppm (5 mg/m³).
Immediately dangerous to life and health (IDLH) limit = 100 ppm (250 mg/m³).
Listed as a potential occupational carcinogen.

References

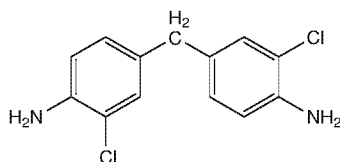
- ACGIH. 2009. *2009 TLVs and BEIs*. Cincinnati, OH: American Conference of Governmental Industrial Hygienists. 256 pp.
- Akron. 2009. *The Chemical Database*. The Department of Chemistry at the University of Akron. <http://uakron.edu/chem/chemdb/> and search on CAS number. Last accessed: 6/1/09.
- ChemIDplus. 2009. *ChemIDplus Advanced*. National Library of Medicine. <http://chem.sis.nlm.nih.gov/chemidplus/chemidheavy.jsp> and select Registry Number and search on CAS number. Last accessed: 6/1/09.
- ChemSources. 2009. *Chem Sources - Chemical Search*. Chemical Sources International. <http://www.chemsources.com/chemonline.html> and search on methylaziridine. Last accessed: 6/1/09.
- EPA. 2004. *Non-confidential IUR Production Volume Information*. U.S. Environmental Protection Agency. <http://www.epa.gov/oppt/iur/tools/data/2002-vol.html> and search on CAS number.
- HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number. Last accessed: 6/1/09.
- IARC. 1975. 2-Methylaziridine. In *Some Arizidines, N-, S-, and O-Mustards and Selenium*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 9. Lyon, France: International Agency for Research on Cancer. pp. 61-65.
- IARC. 1999. 2-Methylaziridine. In *Re-evaluation of Some Organic Chemicals, Hydrazine, and Hydrogen Peroxide*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 71. Lyon, France: International Agency for Research on Cancer. pp. 1497-1502.
- SRI. 2009. *Directory of Chemical Producers*. Menlo Park, CA: SRI Consulting. Database edition. Last accessed: 6/1/09.
- TRI. 2009. *TRI Explorer Chemical Report*. U.S. Environmental Protection Agency. <http://www.epa.gov/triexplorer> and select 2-Methylaziridine. Last accessed: 6/1/09.
- Weisburger EK, Ulland BM, Nam J. 1981. Carcinogenicity tests of certain environmental and industrial chemicals. *J Natl Cancer Inst* 67(1):75-88.

4,4'-Methylenebis(2-chloroaniline)**CAS No. 101-14-4**

Reasonably anticipated to be a human carcinogen

First listed in the *Third Annual Report on Carcinogens* (1983)

Also known as methylene-bis-*ortho*-chloroaniline, MBOCA, or MOCA

**Carcinogenicity**

4,4'-Methylenebis(2-chloroaniline) is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

4,4'-Methylenebis(2-chloroaniline) caused tumors in two rodent species, at several different tissue sites, and by two different routes of exposure. Dietary administration of 4,4'-methylenebis(2-chloroaniline) caused benign or malignant liver tumors (hepatocellular adenoma or carcinoma) in rats of both sexes and in female mice (IARC

1974). Dietary exposure also caused malignant blood-vessel tumors (hemangiosarcoma) in mice of both sexes, benign and malignant lung tumors (adenoma and adenocarcinoma) in rats of both sexes, and mammary-gland cancer (adenocarcinoma) in female rats. Cancer of the liver (hepatocellular carcinoma) and lung (carcinoma) also were observed in rats (sex not specified) administered 4,4'-methylenebis(2-chloroaniline) by subcutaneous injection.

Since 4,4'-methylenebis(2-chloroaniline) was listed in the *Third Annual Report on Carcinogens*, additional studies in experimental animals have been identified. Dietary administration of 4,4'-methylenebis(2-chloroaniline) to male rats caused cancer of the Zymbal gland (carcinoma) and mammary gland (adenocarcinoma), in addition to liver and lung tumors as reported in earlier studies (Kommineni *et al.* 1979). In female dogs, administration of 4,4'-methylenebis(2-chloroaniline) in capsule form caused cancer of the urinary bladder (transitional-cell carcinoma) and urethra (mixed transitional-cell carcinoma and adenocarcinoma) (Stula *et al.* 1978).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to 4,4'-methylenebis(2-chloroaniline). Since 4,4'-methylenebis(2-chloroaniline) was listed in the *Third Annual Report on Carcinogens*, additional studies in humans have been identified. In studies of workers exposed to 4,4'-methylenebis(2-chloroaniline) in the United States and Taiwan, cases of urinary-bladder cancer were detected in a screening program; however, expected rates of asymptomatic urinary-bladder cancer were not available for comparison (IARC 1993, Chen *et al.* 2005). In a small U.K. cohort of male 4,4'-methylenebis(2-chloroaniline) production workers, one urinary-bladder cancer death was reported, yielding a statistically nonsignificant fivefold increase in mortality and threefold increase in incidence, compared with national rates (Dost *et al.* 2009).

Properties

4,4'-Methylenebis(2-chloroaniline) is a chlorinated aromatic amine that exists at room temperature as a tan to colorless crystalline solid with a faint amine odor (IARC 1993, Akron 2009, HSDB 2010). It is practically insoluble in water; soluble in oxygenated solvents, trichloroethylene, toluene, ethoxyethyl acetate, methyl ethyl ketone, tetrahydrofuran, acetone, esters, aromatic hydrocarbons, dimethyl sulfoxide, dimethyl formamide, dilute acids, and carbon tetrachloride; and very soluble in benzene, diethyl ether, and ethanol. When heated to over 200°C, 4,4'-methylenebis(2-chloroaniline) undergoes an exothermic and self-sustaining decomposition reaction, which in a closed container can cause an explosion (Akron 2009). Physical and chemical properties of 4,4'-methylenebis(2-chloroaniline) are listed in the following table.

Property	Information
Molecular weight	267.0 ^a
Specific gravity	1.44 ^a
Melting point	110°C ^a
Boiling point	378.9°C ^b
Log <i>K</i> _{ow}	3.91 ^a
Water solubility	13.9 mg/L at 24°C ^b
Vapor pressure	2.86 × 10 ⁻⁷ mm Hg at 25°C ^a

Sources: ^aHSDB 2010, ^bChemID Plus 2009.

Use

4,4'-Methylenebis(2-chloroaniline) has been used primarily as a curing agent for isocyanate polymers and polyurethane prepolymers in the manufacture of castable urethane rubber products such as indus-

trial tires and rollers, shock-absorption pads, and conveyor belting (IARC 1993, HSDB 2010). It is also used as a curing agent for epoxy. The cured polymers have many uses, including the manufacture of gun mounts, jet engine turbine blades, radar systems, and components in home appliances. In the laboratory, 4,4'-methylenebis(2-chloroaniline) has been used as a positive control for studying mutagens and carcinogens (HSDB 2010).

Production

Production of 4,4'-methylenebis(2-chloroaniline) was first reported in the United States in 1956 (IARC 1974). In 2010, 4,4'-methylenebis(2-chloroaniline) was produced by three manufacturers in east Asia, one manufacturer each in China and Europe, and none in the United States (SRI 2010) and was available from 24 suppliers, including 12 U.S. suppliers (ChemSources 2010). U.S. imports of 4,4'-methylenebis(2-chloroaniline) totaled over 1.9 million pounds in 1989 (HSDB 2010) and almost 2.0 million pounds in 1991 (ATSDR 1994). Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of 4,4'-methylenebis(2-chloroaniline) totaled between 1 million to 10 million pounds from 1986 to 1998, falling to between 500,000 lb and 1 million pounds in 2002 and 2006 (EPA 2004, 2009).

Exposure

The primary route of potential human exposure to 4,4'-methylenebis(2-chloroaniline) is dermal contact; other potential routes are inhalation and ingestion (IARC 1993). According to EPA's Toxics Release Inventory, environmental releases of 4,4'-methylenebis(2-chloroaniline) since 1988 have ranged from lows of 19 lb in 1992 and 26 lb in 1998 to highs of 14,933 lb in 1993 and 26,185 lb in 2000. Releases fell to 14,719 lb in 2001 and 1,708 lb in 2002, remaining around 2,000 lb from 2002 to 2004. Most releases before 1999 were to air; since then, most releases have been to land. In 2005, 5,000 lb of 4,4'-methylenebis(2-chloroaniline) was released to air and to off-site landfills. The release total and pattern remained similar through 2007, when five facilities released a total of 6,233 lb (TRI 2010). 4,4'-Methylenebis(2-chloroaniline) has been identified in at least four hazardous-waste sites on the National Priorities List (ATSDR 1994).

When released to air, 4,4'-methylenebis(2-chloroaniline) will exist mainly as a particulate that is removed by dry and wet deposition; the portion that remains in the vapor phase will react with hydroxyl radicals, with a half-life of 5 hours. If released to surface water, 4,4'-methylenebis(2-chloroaniline) is likely to be strongly adsorbed to organic matter or may be photodegraded in surface water, but is not easily hydrolyzed. If released to soil, it will bind to soil particles and will have slight mobility in the subsurface environment; however, it may be subject to aerobic biodegradation. It may bioaccumulate in food plants but is not readily translocated through the plant (ATSDR 1994, HSDB 2010).

In 1979, 4,4'-methylenebis(2-chloroaniline) was detected in soil samples obtained within a 1-km (0.6-mi) radius of a chemical plant in Michigan; concentrations in soil samples from along public roads in the area were as high as 590 ppm. Concentrations of 4,4'-methylenebis(2-chloroaniline) were as high as 18 ppm in sludge from the wastewater-treatment plant in the area and over 1,600 ppm in sediment from an on-site industrial lagoon (ATSDR 1994).

The risk of exposure to 4,4'-methylenebis(2-chloroaniline) is greatest for workers involved in the manufacture of polyurethane and plastic products where 4,4'-methylenebis(2-chloroaniline) is used as a curing agent (ATSDR 1994). When used for this purpose, 4,4'-methylenebis(2-chloroaniline) is melted before being mixed

into an elastomer formulation; it potentially could volatilize and be emitted into waste gases and wastewater (IARC 1993, ATSDR 1994, TRI 2010). Urine from workers at polyurethane plastics manufacturing facilities in the United Kingdom, France, and Australia contained 4,4'-methylenebis(2-chloroaniline) at concentrations as high as 1.3 mg/L of urine (IARC 1993, ATSDR 1994, Vaughan and Kenyon 1996, Robert *et al.* 1999a,b). In 2006, the U.S. Occupational Safety and Health Administration conducted an occupational exposure investigation of a small U.S. company that manufactured pliable polyurethane parts. Surface wipe samples collected from the top of the metal scale table were reported to have concentrations of 4,4'-methylenebis(2-chloroaniline) as high as 209 µg/m², and total 4,4'-methylenebis(2-chloroaniline) was measured in the urine of one worker at a concentration of 15 µg/L (Fairfax and Porter 2006). In a manufacturing facility in Taiwan, 4,4'-methylenebis(2-chloroaniline) was found in the air at concentrations of up to 0.41 mg/m³ (410 µg/m³) (Chen *et al.* 2005), and concentrations in the urine of 10 workers ranged from 267.9 to 15,701.1 µg/g of creatinine (mean = 5,544 µg/g) (Liu *et al.* 2005).

Regulations

Department of Transportation (DOT)

4,4'-Methylenebis(2-chloroaniline) is considered a hazardous material, and special requirements have been set for transporting this material in tank cars.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of 4,4'-methylenebis(2-chloroaniline) = U158.

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

4,4'-Methylenebis(2-chloroaniline) is prohibited from indirect addition to human food through food-contact surfaces; food containing any added or detectable level of this substance is prohibited.

4,4'-Methylenebis(2-chloroaniline) may be used as antioxidants and/or stabilizers for polymers in indirect food additives as prescribed in 21 CFR 178.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.01 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 0.003 mg/m³.

Listed as a potential occupational carcinogen.

References

- Akron. 2009. *The Chemical Database*. The Department of Chemistry at the University of Akron. <http://ull.chemistry.uakron.edu/erd> and search on CAS number. Last accessed: 12/18/09.
- ATSDR. 1994. *Toxicological Profile for 4,4'-Methylenebis(2-chloroaniline)*. MBOCA. Agency for Toxic Substances and Disease Registry. <http://www.atsdr.cdc.gov/toxprofiles/tp45.pdf>.
- ChemIDplus. 2009. *ChemIDplus Advanced*. National Library of Medicine. <http://chem.sis.nlm.nih.gov/chemidplus/chemidheavy.jsp> and select Registry Number and search on CAS number. Last accessed: 9/30/09.
- ChemSources. 2010. *Chem Sources - Chemical Search*. Chemical Sources International. <http://www.chemsources.com/chemonline.html> and search on methylenebischloroaniline. Last accessed: 1/10.
- Chen HI, Liou SH, Loh CH, Uang SN, Yu YC, Shih TS. 2005. Bladder cancer screening and monitoring of 4,4'-methylenebis(2-chloroaniline) exposure among workers in Taiwan. *Urology* 66(2): 305-310.
- Dost A, Straughan JK, Sorahan T. 2009. Cancer incidence and exposure to 4,4'-methylene-bis-ortho-chloroaniline (MbOCA). *Occup Med (Lond)* 59(6): 402-405.
- EPA. 2004. *Non-confidential IUR Protection Volume Information*. U.S. Environmental Protection Agency. <http://www.epa.gov/oppt/iur/tools/data/2002-vol.html> and search on CAS number.

EPA. 2009. *Non-confidential 2006 IUR Records by Chemical, Including Manufacturing, Processing and Use Information*. U.S. Environmental Protection Agency. http://cfpub.epa.gov/iursearch/2006_iur_natlcheminfo.cfm?id=1099.

Fairfax R, Porter E. 2006. Evaluation of worker exposure to TDI, MOCA, and methylene chloride. *J Occup Environ Hyg* 3(6): D50-D53.

HSDB. 2010. *Hazardous Substances Data Bank*. National Library of Medicine. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number. Last accessed: 1/10.

IARC. 1974. 4,4'-Methylene bis(2-chloroaniline). In *Some Aromatic Amines, Hydrazine and Related Substances, N-Nitroso Compounds and Miscellaneous Alkylating Agents*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 4. Lyon, France: International Agency for Research on Cancer, pp. 65-71.

IARC. 1993. 4,4'-Methylene bis(2-chloroaniline) (MOCA). In *Occupational Exposures of Hairdressers and Barbers and Personal Use of Hair Colourants*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 57. Lyon, France: International Agency for Research on Cancer, pp. 271-303.

Komminen C, Groth DH, Frockt JJ, Voelker RW, Stanovick RP. 1979. Determination of the tumorigenic potential of methylene-bis-ortho-chloroaniline. *J Environ Pathol Toxicol* 2(5): 149-171.

Liu CS, Liou SH, Loh CH, Yu YC, Ueng SN, Shih TS, Chen HI. 2005. Occupational bladder cancer in a 4,4'-methylenebis(2-chloroaniline) (MBOCA)-exposed worker. *Environ Health Perspect* 113(6): 771-774.

Robert A, Ducos P, Francin JM. 1999a. Biological monitoring of workers exposed to 4,4'-methylene-bis-(2-ortho-chloroaniline) (MOCA). I. A new and easy determination of "free" and "total" MOCA in urine. *Int Arch Occup Environ Health* 72(4): 223-238.

Robert A, Ducos P, Francin JM. 1999b. Biological monitoring of workers exposed to 4,4'-methylene-bis-(2-ortho-chloroaniline) (MOCA). II. Comparative interest of "free" and "total" MOCA in the urine of exposed workers. *Int Arch Occup Environ Health* 72(4): 229-237.

SRI. 2010. *Directory of Chemical Producers*. Menlo Park, CA: SRI Consulting. Database edition. Last accessed: 1/10.

Stula EF, Barnes JR, Sherman H, Reinhardt CF, Zapp JA Jr. 1978. Urinary bladder tumors in dogs from 4,4'-methylene-bis (2-chloroaniline) (MOCA). *J Environ Pathol Toxicol* 1(1): 31-50.

TRI. 2010. *TRI Explorer Chemical Report*. U.S. Environmental Protection Agency. <http://www.epa.gov/triexplorer> and select 4,4'-Methylenebis(2-Chloroaniline). Last accessed: 1/10.

Vaughan GT, Kenyon RS. 1996. Monitoring for occupational exposure to 4,4'-methylenebis(2-chloroaniline) by gas chromatographic-mass spectrometric analysis of haemoglobin adducts, blood, plasma and urine. *J Chromatogr B Biomed Appl* 678(2): 197-204.

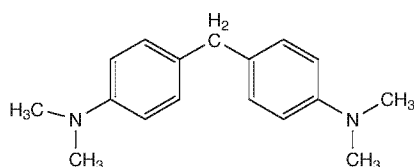
4,4'-Methylenebis(N,N-dimethyl)-benzenamine

CAS No. 101-61-1

Reasonably anticipated to be a human carcinogen

First listed in the *Third Annual Report on Carcinogens* (1983)

Also known as Michler's base or *p,p'*-tetramethyldiaminodiphenylmethane



Carcinogenicity

4,4'-Methylenebis(N,N-dimethyl)benzenamine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to 4,4'-methylenebis(N,N-dimethyl)benzenamine caused tumors in two rodent species and at two different tissue sites. Dietary administration of 4,4'-methylenebis(N,N-dimethyl)benzenamine caused cancer of the thyroid gland (follicular-cell carcinoma) in rats of both sexes and increased the combined incidence of benign and malignant liver tumors (hepatocellular adenoma and carcinoma) in female mice (NCI 1979).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to 4,4'-methylenebis(N,N-dimethyl)benzenamine.

Properties

4,4'-Methylenebis(N,N-dimethyl)benzenamine is a bicyclic aromatic amine that exists at room temperature as yellowish glistening leaflets or plates or as tan crystals with a faint odor (NCI 1979, Akron 2009, HSDB 2009). Commonly referred to as Michler's base, it is the reduced form of Michler's ketone, which is listed in the Report on Carcinogens as *reasonably anticipated to be a human carcinogen*. 4,4'-Methylenebis(N,N-dimethyl)benzenamine is practically insoluble in water, slightly soluble in cold alcohol, and soluble in hot alcohol, benzene, diethyl ether, carbon disulfide, and acids (ChemIDplus 2009, HSDB 2009). It is stable under normal temperatures and pressures (Akron 2009). Physical and chemical properties of 4,4'-methylenebis(N,N-dimethyl)benzenamine are listed in the following table.

Property	Information
Molecular weight	254.4 ^a
Density	1.14 g/cm ³ at 20°C ^b
Melting point	90°C to 91°C ^a
Boiling point	390°C ^a
Log <i>K</i> _{ow}	4.37 ^c
Water solubility	4.14 mg/L at 25°C ^c
Vapor pressure	1.75 × 10 ⁻⁵ mm Hg at 25°C ^c
Vapor density relative to air	8.77 ^b

Sources: ^aHSDB 2009, ^bAkron 2009, ^cChemIDplus 2009.

Use

4,4'-Methylenebis(N,N-dimethyl)benzenamine is used as an intermediate in the manufacture of at least six dyes and one pigment (including methylene red and C.I. basic yellow 2, basic orange 14, solvent orange 15, and solvent yellow 34). Its hydrochloride salt is used as an analytical reagent for the determination of lead (IARC 1982).

Production

Commercial production of 4,4'-methylenebis(N,N-dimethyl)benzenamine in the United States began in the early 1920s (IARC 1982). U.S. production was approximately 1.8 million pounds in 1974, decreasing to 1.0 million pounds in 1977. In 2009, 4,4'-methylenebis(N,N-dimethyl)benzenamine was produced by one manufacturer each in China, Europe, and India (SRI 2009) and was available from 16 suppliers, including 10 U.S. suppliers (ChemSources 2009). Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of 4,4'-methylenebis(N,N-dimethyl)benzenamine totaled 500,000 lb to 1 million pounds in 1986 and 10,000 to 500,000 lb in 1990 (EPA 2004); no inventory update reports for 4,4'-methylenebis(N,N-dimethyl)benzenamine were filed in 1994, 1998, or 2002.

Exposure

The routes of potential human exposure to 4,4'-methylenebis(N,N-dimethyl)benzenamine are inhalation, ingestion, and dermal contact (NJDHSS 2009). EPA's Toxics Release Inventory reported environmental releases of 8,400 lb in 1988, 10 lb in 1995, and 1 lb in 1996; no more recent releases have been reported (TRI 2009). Although the compound is relatively nonvolatile, workers may be exposed via inhalation of dust. The potential for exposure is greatest among workers in the dye and chemical manufacturing industries (NCI 1979).

The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 4,140 workers potentially were exposed to 4,4'-methylenedis(N,N-dimethyl)benzenamine (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

References

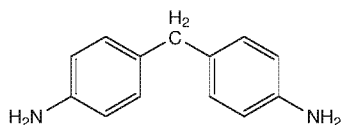
- Akron. 2009. *The Chemical Database*. The Department of Chemistry at the University of Akron. <http://uakron.edu/chem/erd> and search on CAS number. Last accessed: 8/11/09.
- ChemIDplus. 2009. *ChemIDplus Advanced*. National Library of Medicine. <http://chem.sis.nlm.nih.gov/chemidplus/chemidheavy.jsp> and select Registry Number and search on CAS number. Last accessed: 8/11/09.
- ChemSources. 2009. *Chem Sources - Chemical Search*. Chemical Sources International. <http://www.chemsources.com/chemonline.html> and search on tetramethyldiaminodiphenylmethane. Last accessed: 8/11/09.
- EPA. 2004. *Non-confidential IUR Production Volume Information*. U.S. Environmental Protection Agency. <http://www.epa.gov/oppt/iuri/tools/data/2002-vol.html> and search on CAS number. Last accessed: 4/21/05.
- HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number. Last accessed: 8/11/09.
- IARC. 1982. 4,4'-Methylenedis(N,N-dimethyl)benzenamine. In *Some Aromatic Amines, Anthraquinones and Nitroso Compounds and Inorganic Fluorides Used in Drinking Water and Dental Preparations*, vol. 27. Lyon, France: International Agency for Research on Cancer. pp. 119-126.
- NCI. 1979. *Bioassay of 4,4'-Methylenedis(N,N-dimethyl)benzenamine for Possible Carcinogenicity*. Technical Report Series no. 186. DHEW (NIH) Publication No. 79-1742. Bethesda, MD: National Institutes of Health. 110 pp.
- NIOSH. 1990. *National Occupational Exposure Survey (1981-83)*. National Institute for Occupational Safety and Health. Last updated: 1990. <http://www.cdc.gov/noes/noes1/m3405sic.html>. Last accessed: 1/24/05.
- NJDHSS. 2009. *Hazardous Substance Fact Sheet: 4,4'-Methylenedis(N,N-Dimethyl)Benzenamine*. New Jersey Department of Health & Senior Services. <http://nj.gov/health/eoh/rtkweb/documents/fs/1252.pdf>.
- SRI. 2009. *Directory of Chemical Producers*. Menlo Park, CA: SRI Consulting. Database edition. Last accessed: 8/11/09.
- TRI. 2009. *TRI Explorer Chemical Report*. U.S. Environmental Protection Agency. <http://www.epa.gov/triexplorer> and select 4,4'-Methylenedis(N,N-Dimethyl)benzenamine.

4,4'-Methylenedianiline and Its Dihydrochloride

CAS Nos. 101-77-9 and 13552-44-8

Reasonably anticipated to be human carcinogens

First listed in the *Fourth Annual Report on Carcinogens* (1985)



Carcinogenicity

4,4'-Methylenedianiline and its dihydrochloride salt are *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to 4,4'-methylenedianiline dihydrochloride caused tumors at several different tissue sites in mice and rats. Administration of 4,4'-methylenedianiline dihydrochloride in the drinking water caused benign and/or malignant tumors of the thyroid gland (C-cell adenoma or follicular-cell adenoma or carcinoma) in mice and rats of both sexes and benign or malignant liver tumors (hepatocellular adenoma or carcinoma) in mice of both sexes and in male rats.

It also caused malignant lymphoma in female mice and benign adrenal-gland tumors (pheochromocytoma) in male mice (NTP 1983).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to 4,4'-methylenedianiline or its dihydrochloride.

Properties

4,4'-Methylenedianiline is an aromatic amine that exists at room temperature as colorless to pale yellow to tan flakes or lumps with a faint amine-like odor (IARC 1986, Akron 2009, HSDB 2009). 4,4'-Methylenedianiline is only slightly soluble in water, but soluble in ethanol, benzene, diethyl ether, and acetone. The dihydrochloride salt is soluble in water. 4,4'-Methylenedianiline is stable at normal temperatures and pressures (Akron 2009). Physical and chemical properties of 4,4'-methylenedianiline are listed in the following table.

Property	Information
Molecular weight	198.3 ^a
Specific gravity	1.056 at 100°C/4°C ^a
Melting point	91.5°C to 92°C ^a
Boiling point	398°C to 399°C at 768 mm Hg ^a
Log <i>K</i> _{ow}	1.59 ^a
Water solubility	1 g/L at 25°C ^b
Vapor pressure	1 mm Hg at 197°C ^a
Vapor density relative to air	6.8 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

More than 90% of the 4,4'-methylenedianiline produced in the United States is used as a chemical intermediate in the closed-system production of 4,4'-methylenedianiline diisocyanate and polyisocyanates (NTP 1983, IARC 1986). These products are used to produce a variety of polymers and resins, such as polyurethane foam, elastomers (e.g., Spandex fibers), and isocyanate resins. 4,4'-Methylenedianiline is also used as a cross-linking agent for epoxy resins, and the U.S. Food and Drug Administration has approved the use of these epoxy resins to coat containers for beverages having an alcohol content of up to 8%. 4,4'-Methylenedianiline is also used as an analytical reagent for analysis, including the determination of tungsten and sulfates, as a corrosion inhibitor, as an antioxidant and curative agent in rubber, and to prepare azo dyes (IARC 1986, ATSDR 1998). No data were available on the use of the dihydrochloride salt.

Production

4,4'-Methylenedianiline has been produced commercially in the United States since the early 1920s (IARC 1986). It is available in bulk quantities containing approximately 96% 4,4'-methylenedianiline, 3% other isomeric amines, and traces of aniline (ATSDR 1998). In the early 1980s, six or seven manufacturers produced between 200 million and 400 million pounds of 4,4'-methylenedianiline per year. In 1987, about 600 million pounds was produced and used captively as a chemical intermediate, 4.5 million pounds was produced domestically for sale, and 1.8 million pounds was imported (OSHA 1987). In 2009, 4,4'-methylenedianiline was produced by ten manufacturers worldwide, including one in the United States (SRI 2009), and was available from 28 suppliers, including 14 U.S. suppliers (ChemSources 2009). No producers or suppliers of the hydrochloride salt were identified. From 1989 to 1993, U.S. imports of 4,4'-methylenedianiline were 3.3, 2.9, 2.4, 2.0, and 1.1 million pounds, and U.S. exports were 28.9, 29.8, 12.8, 15.7, and 9.9 million pounds (ATSDR 1998). Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Con-

trol Act Inventory Update Rule indicated that U.S. production plus imports of 4,4'-methylenedianiline totaled 100 million to 500 million pounds in 1986, falling to between 1 million and 10 million pounds in 1990, remaining in that range in through 2002 (EPA 2004), and returning to between 100 million and 500 million pounds in 2006 (EPA 2009). No data on U.S. production, imports, or exports of the dihydrochloride salt were found.

Exposure

Although most exposure to 4,4'-methylenedianiline is occupational, the general population may be exposed through dermal contact with trace amounts present in consumer products made from polyurethane foam, Spandex, and epoxy-containing products. Although 4,4'-methylenedianiline may be used in their production, very little of the chemical is present in its free state in the final products. Levels of 4,4'-methylenedianiline in food and food packaging are so low that exposure is unlikely. Polyurethane is used in medical devices, and exposure may occur from small releases of 4,4'-methylenedianiline during sterilization with gamma radiation; patients most likely to be exposed from this source are those receiving frequent blood transfusions or undergoing kidney dialysis (ATSDR 1998).

4,4'-Methylenedianiline may be released to the environment during industrial production and use (IARC 1986, ATSDR 1998). Very few data were available regarding concentrations of 4,4'-methylenedianiline in ambient air, surface water, industrial effluents, or soil. According to EPA's Toxics Release Inventory, environmental releases of 4,4'-methylenedianiline declined from 736,000 lb in 1988 to 29,000 lb in 1992 and remained between 29,000 and 78,000 lb through 2003. Releases increased in 2004, reaching 207,176 lb in 2005, and then decreased, reaching 67,423 lb in 2007. In 2007, 58,000 lb of 4,4'-methylenedianiline was released from one facility to an underground injection well, and most of the remainder was released to air. Reporting is not required for the hydrochloride salt (TRI 2009). If 4,4'-methylenedianiline is released to air, the vapor phase will be degraded by photochemically produced hydroxyl radicals, with a half-life of 1.6 hours (HSDB 2009). If released to soil, 4,4'-methylenedianiline will covalently bind to humic material, but will leach from soil without humic material. If released to water, 4,4'-methylenedianiline may covalently bind to suspended solids and sediments containing humic material. On the water surface, it will be susceptible to degradation by photochemically produced hydroxyl and peroxy radicals, with a half-life of 19 to 30 hours.

The primary routes of potential occupational exposure to 4,4'-methylenedianiline are inhalation and dermal contact. Workers may be exposed while producing, formulating, and packaging the chemical, during its use, and from hydrolysis of 4,4'-methylenedianiline diisocyanate. No 4,4'-methylenedianiline is released during autoclave sterilization of medical equipment (IARC 1986, ATSDR 1998). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that over 15,000 workers, including about 3,400 women, potentially were exposed to 4,4'-methylenedianiline (NIOSH 1990). In 1992, the Occupational Safety and Health Administration estimated that 3,836 workers in 11 principal industry sectors were exposed to 4,4'-methylenedianiline (OSHA 1992), at air concentrations ranging from 1 to 250 ppb and for average annual exposure durations of 47 to 250 days. 4,4'-Methylenedianiline was measured at concentrations of up to 31 mg/m³ in air inside facilities where it was produced and up to 1.6 mg/m³ inside fabrication facilities while it was being used. It was detected in the urine of 4 of 27 production workers (14.9%) at concentrations of at least 200 µg/L in 1970, but in the urine of only 0.09% of workers (numbers not reported) at concentrations of 20 µg/L or less in 1980 (IARC 1986, ATSDR 1998). In a

2005 risk assessment, the concentration of 4,4'-methylenedianiline in freshly produced polyurethane foam was 2 to 3.5 mg/kg at the time of demolding, declining to 1 mg/kg one hour after demolding and continuing to decline slowly over time (Lewandowski *et al.* 2005); based on these concentrations, cancer risks from dermal exposure were found to be below the level of concern. It was assumed that adequate ventilation would minimize inhalation exposure.

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: 4,4'-Methylenedianiline is listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture of 4,4'-methylenedianiline is subject to certain provisions for the control of volatile organic compound emissions.

Comprehensive Environmental Response, Compensation, and Liability Act
Reportable quantity (RQ) = 10 lb for 4,4'-methylenedianiline.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: 4,4'-Methylenedianiline is a listed substance subject to reporting requirements.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 0.010 ppm for 4,4'-methylenedianiline.

Short-term exposure limit (STEL) = 0.10 ppm for 4,4'-methylenedianiline.

Comprehensive standards have been developed for occupational exposure to 4,4'-methylenedianiline and its salts.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.1 ppm for 4,4'-methylenedianiline.

National Institute for Occupational Safety and Health (NIOSH)

4,4'-Methylenedianiline is listed as a potential occupational carcinogen.

References

- Akron. 2009. *The Chemical Database*. The Department of Chemistry at the University of Akron. <http://uakron.edu/chem> and search on CAS number. Last accessed: 7/13/2009.
- ATSDR. 1998. *Toxicological Profile for Methylenedianiline*. Agency for Toxic Substances and Disease Registry. <http://www.atsdr.cdc.gov/toxprofiles/tp122.pdf>.
- ChemIDplus. 2009. *ChemIDplus Advanced*. National Library of Medicine. <http://chem.sis.nlm.nih.gov/chemidplus/chemidheavy.jsp> and select Registry Number and search on CAS number. Last accessed: 7/13/2009.
- ChemSources. 2009. *Chem Sources - Chemical Search*. Chemical Sources International. <http://www.chemsources.com/chemonline.html> and search on methylenedianiline. Last accessed: 7/13/2009.
- EPA. 2004. *Non-confidential IUR Production Volume Information*. U.S. Environmental Protection Agency. <http://www.epa.gov/oppt/iur/tools/data/2002-vol.html> and search on CAS number.
- EPA. 2009. *Non-confidential 2006 IUR Records by Chemical, Including Manufacturing, Processing and Use Information*. U.S. Environmental Protection Agency. http://cfpub.epa.gov/iursearch/2006_iur_natlcheminfo.cfm?id=79.
- HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number. Last accessed: 7/13/2009.
- IARC. 1986. 4,4'-Methylenedianiline and its dihydrochloride. In *Some Chemicals Used in Plastics and Elastomers*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 39. Lyon, France: International Agency for Research on Cancer. pp. 347-365.
- Lewandowski TA, Hayes AW, Beck BD. 2005. Risk evaluation of occupational exposure to methylenedianiline and toluene diamine in polyurethane foam. *Hum Exp Toxicol* 24(12): 655-662.
- NIOSH. 1990. *National Occupational Exposure Survey (1981-83)*. National Institute for Occupational Safety and Health. Last updated: 7/1/90. <http://www.cdc.gov/noes/noes1/83609sic.html>.
- NTP. 1983. *Carcinogenesis Studies of 4,4'-Methylenedianiline Dihydrochloride (CAS No. 13552-44-8) in F344/N Rats and B6C3F₁ Mice (Drinking Water Studies)*. Technical Report Series no. 448. Research Triangle Park, NC: National Toxicology Program. 182 pp.
- OSHA. 1987. Methylenedianiline, 4,4-. Proposed rules. *Fed Regist* 52: 26776-26903.
- OSHA. 1992. Occupational exposure to 4,4'-methylenedianiline (MDA) (1910.1050); Final rule. *Fed Regist* 57: 35630.
- SRI. 2009. *Directory of Chemical Producers*. Menlo Park, CA: SRI Consulting. Database edition. Last accessed: 7/13/2009.

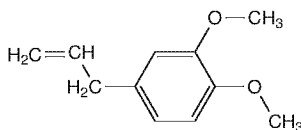
TRI. 2009. TRI Explorer Chemical Report. U.S. Environmental Protection Agency. <http://www.epa.gov/triexplorer> and select 4,4'-Methylenedianiline. Last accessed: 7/13/2009.

Methyleugenol

CAS No. 93-15-2

Reasonably anticipated to be a human carcinogen

First listed in the *Tenth Report on Carcinogens* (2002)



Carcinogenicity

Methyleugenol is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to methyleugenol caused tumors in two rodent species and at several different tissue sites. Methyleugenol administered by stomach tube caused benign or malignant liver tumors (hepatocellular adenoma or carcinoma) in rats and mice of both sexes. In rats, methyleugenol also caused benign or malignant stomach tumors (neuroendocrine tumors) in both sexes and tumors of the kidney (renal-tubule adenoma), mammary gland (fibroadenoma), and skin (fibroma or fibrosarcoma) in males. Malignant neuroendocrine tumors of the stomach in male mice also were considered to be related to methyleugenol exposure (NTP 2000). Earlier studies found that methyleugenol and two structurally related allylbenzenes, safrole and estragole, caused liver tumors in mice when administered by intraperitoneal injection (IARC 1976, Miller *et al.* 1983). Safrole is listed in the Report on Carcinogens as *reasonably anticipated to be a human carcinogen* and by the International Agency for Research on Cancer as possibly carcinogenic to humans.

Studies on Mechanisms of Carcinogenesis

Mechanistic studies indicate that liver tumors induced by methyleugenol and structurally related allylbenzenes result from metabolism of these compounds to DNA-reactive intermediates. Methyleugenol may be bioactivated by three different pathways: (1) hydroxylation at the 1' position of the allylic side chain to yield 1'-hydroxymethyleugenol, followed by sulfation of this intermediate to form 1'-hydroxymethyleugenol sulfate, (2) oxidation of the 2',3'-double bond of the allylic side chain to form methyleugenol-2,3-oxide, and (3) O-demethylation followed by spontaneous rearrangement to form eugenol quinone methide. Formation of protein adducts and DNA adducts in the livers of animals (and in cultured human hepatocytes) exposed to allylbenzenes and induction of liver tumors by these compounds in animals have been attributed to activation via the hydroxylation pathway, because similar effects were produced by the 1'-hydroxy metabolites and because these effects were inhibited by pretreatment with sulfotransferase inhibitors (Boberg *et al.* 1983, Miller *et al.* 1983, Randerath *et al.* 1984, Gardner *et al.* 1996, NTP 2000).

Methyleugenol, safrole, and estragole caused unscheduled DNA synthesis in rat hepatocytes, and their corresponding 1'-hydroxy metabolites were more potent genotoxic agents than were the parent compounds (Howes *et al.* 1990, Chan and Caldwell 1992). Methyleugenol caused morphological transformation of Syrian hamster

embryo cells (Kerckaert *et al.* 1996), sister chromatid exchange in Chinese hamster ovary (CHO) cells (NTP 2000), intrachromosomal recombination in yeast (Schiestl *et al.* 1989), and DNA repair in *Bacillus subtilis* (Sekizawa and Shibamoto 1982). It did not cause mutations in *Salmonella typhimurium* (NTP 2000) or *Escherichia coli* (Sekizawa and Shibamoto 1982), chromosomal aberrations in CHO cells (NTP 2000), or micronucleus formation in the peripheral-blood erythrocytes of mice (NTP 2000). A higher frequency of β -catenin mutations was observed in liver tumors from mice exposed to methyleugenol than in spontaneous liver tumors from unexposed mice (Devereux *et al.* 1999). Methyleugenol's lack of mutagenicity in bacteria may be due to the need for sulfation in the metabolic activation of methyleugenol to its ultimate mutagenic or carcinogenic form.

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to methyleugenol.

Properties

Methyleugenol is an allyl-chain-substituted guaiacol that structurally resembles safrole (NTP 2000). It is a colorless to pale yellow, oily liquid with an odor of cloves and carnations. It is insoluble in water, glycol, and propylene glycol and soluble in ethanol, ethyl ether, chloroform, and many other organic solvents. Methyleugenol is unstable at room temperature; it darkens and thickens when exposed to air and readily evaporates at room temperature (NTP 2000). Physical and chemical properties of methyleugenol are listed in the following table.

Property	Information
Molecular weight	178.2 ^a
Specific gravity	1.0396 at 20°C/4°C ^a
Melting point	-4°C ^a
Boiling point	254.7°C at 760 mm Hg ^a
Log K_{ow}	3.03 ^b
Water solubility	0.500 g/L at 25°C ^b
Vapor pressure	1 mm Hg at 85.0°C ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Methyleugenol is used in fragrances and as a flavoring agent in jellies, baked goods, nonalcoholic beverages, chewing gum, candy, pudding, relish, and ice cream. It is also used as an insect attractant in combination with insecticides and has been used as an anesthetic in rodents (NTP 2000, HSDB 2009).

Production

Annual production of methyleugenol in the United States in 1990 was estimated at 25,000 lb (NTP 2000). No current production data were found.

Exposure

The general population may be exposed to methyleugenol through ingestion of foods or inhalation of fragrances containing the compound (HSDB 2009). Methyleugenol is a naturally occurring substance, present in many essential oils, including the oils of rose, pimento, basil, hyacinth, citronella, anise, nutmeg, mace, cinnamon leaves, pixuri seeds, and laurel fruits and leaves. It has also been found in blackberry essence, bananas, black pepper, and bilberries (NTP 2000). Methyleugenol is used in commercial products as a flavorant at concentrations of 5 to 52 ppm and in fragrances at concentrations of 0.002% to 0.3% (HSDB 2009). In a subset of serum samples from adults participating in the third National Health and Nutrition Examination

Survey, methyleugenol was detected in 98% of the 206 samples analyzed. The average methyleugenol concentration was 24 pg/g, and the highest concentration was 390 pg/g (Barr *et al.* 2000). Daily per-capita consumption of methyleugenol in food was estimated by the World Health Organization to be 0.073 mg (WHO 1981) and, more recently, 0.26 mg/kg of body weight (Stroberg and Grundschober 1987, NAS 1989).

Although methyleugenol has been identified in various natural substances, no quantitative studies were found that assessed environmental (nondietary) exposure to methyleugenol. In air, methyl-eugenol exists as a vapor; it reacts with photochemically produced hydroxyl radicals and degrades with an estimated half-life of 5 hours (HSDB 2009). Methyleugenol has been detected in wastewater effluent from a paper mill (NTP 2000).

Occupational exposure to methyleugenol may occur through dermal contact, inhalation, and ingestion. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 12,682 workers, including 9,413 women, potentially were exposed to methyl-eugenol (NIOSH 1990).

Regulations

No specific regulations or guidelines relevant to reduction of exposure to methyleugenol were identified.

References

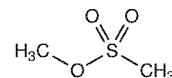
- Barr DB, Barr JR, Bailey SL, Lapeza CR, Jr, Beeson MD, Caudill SP, *et al.* 2000. Levels of methyleugenol in a subset of adults in the general U.S. population as determined by high resolution mass spectrometry. *Environ Health Perspect* 108(4): 323-328.
- Boberg EW, Miller EC, Miller JA, Poland A, Liem A. 1983. Strong evidence from studies with brachyomorphic mice and pentachlorophenol that 1'-sulfoxysafrole is the major ultimate electrophilic and carcinogenic metabolite of 1'-hydroxysafrole in mouse liver. *Cancer Res* 43(11): 5163-5173.
- Chan VS, Caldwell J. 1992. Comparative induction of unscheduled DNA synthesis in cultured rat hepatocytes by allylbenzenes and their 1'-hydroxy metabolites. *Food Chem Toxicol* 30(10): 831-836.
- ChemIDplus. 2009. *ChemIDplus Advanced*. National Library of Medicine. <http://chem.sis.nlm.nih.gov/chemidplus/chemidheavy.jsp> and search on CAS number. Last accessed: 10/22/09.
- Devereux TR, Anna CH, Foley JF, White CM, Sills RC, Barrett JC. 1999. Mutation of beta-catenin is an early event in chemically induced mouse hepatocellular carcinogenesis. *Oncogene* 18(33): 4726-4733.
- Gardner I, Bergin P, Stening P, Kenna JG, Caldwell J. 1996. Immunochemical detection of covalently modified protein adducts in livers of rats treated with methyleugenol. *Chem Res Toxicol* 9(4): 713-721.
- Howes AJ, Chan VS, Caldwell J. 1990. Structure-specificity of the genotoxicity of some naturally occurring alkenylbenzenes determined by the unscheduled DNA synthesis assay in rat hepatocytes. *Food Chem Toxicol* 28(8): 537-542.
- HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number. Last accessed: 10/22/09.
- IARC. 1976. Safrole, isosafrole and dihydrosafrole. In *Some Naturally Occurring Substances*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 10. Lyon, France: International Agency for Research on Cancer. pp. 231-244.
- Kerckaert GA, Brauning R, LeBoeuf RA, Isfort RJ. 1996. Use of the Syrian hamster embryo cell transformation assay for carcinogenicity prediction of chemicals currently being tested by the National Toxicology Program in rodent bioassays. *Environ Health Perspect* 104(Suppl 5): 1075-1084.
- Miller EC, Swanson AB, Phillips DH, Fletcher TL, Liem A, Miller JA. 1983. Structure-activity studies of the carcinogenicities in the mouse and rat of some naturally occurring and synthetic alkenylbenzene derivatives related to safrole and estragole. *Cancer Res* 43(3): 1124-1134.
- NAS. 1989. *Poundage and Technical Effects Update of Substances Added to Food*. Committee on Food Additives Survey Data, Food and Nutrition Board, Institute of Medicine. Washington, DC: National Academy of Sciences.
- NIOSH. 1990. *National Occupational Exposure Survey (1981-83)*. National Institute for Occupational Safety and Health. Last updated 7/1/90. <http://www.cdc.gov/noes/noes1/04500sic.html>.
- NTP. 2000. *Toxicology and Carcinogenesis Studies of Methyleugenol (CAS NO. 93-15-2) in F344/N Rats and B6C3F₁ Mice (Gavage Studies)*. NTP Technical Report Series no. 491. Research Triangle Park, NC: National Toxicology Program. 412 pp.
- Randerath K, Haglund RE, Phillips DH, Reddy MV. 1984. ³²P-post-labelling analysis of DNA adducts formed in the livers of animals treated with safrole, estragole and other naturally-occurring alkenylbenzenes. I. Adult female CD-1 mice. *Carcinogenesis* 5(12): 1613-1622.
- Schiestl RH, Chan WS, Gietz RD, Mehta RD, Hastings PJ. 1989. Safrole, eugenol and methyleugenol induce intrachromosomal recombination in yeast. *Mutat Res* 224(4): 427-436.
- Sekizawa J, Shibamoto T. 1982. Genotoxicity of safrole-related chemicals in microbial test systems. *Mutat Res* 101(2): 127-140.
- Stroberg J, Grundschober F. 1987. Consumption ratio and food predominance of flavoring materials. *Perfum Flavor* 12: 27-56.
- WHO. 1981. *Evaluation of Certain Food Additives and Contaminants. Twenty-sixth Report of the Joint FAO/WHO Expert Committee on Food Additives*. Technical Report Series no. 669. Geneva, Switzerland: World Health Organization. pp. 92-94.

Methyl Methanesulfonate

CAS No. 66-27-3

Reasonably anticipated to be a human carcinogen

First listed in the *Sixth Annual Report on Carcinogens* (1991)



Carcinogenicity

Methyl methanesulfonate is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Methyl methanesulfonate caused tumors in mice and rats at several different tissue sites and by several different routes of exposure. Administration of methyl methanesulfonate in the drinking water caused benign lung tumors (adenoma) and lymphoma of the thymus in male mice. In male rats, subcutaneous injection of methyl methanesulfonate caused cancer at the injection site (squamous-cell carcinoma and polymorphic-cell sarcoma), and 1 of 12 rats developed kidney cancer (nephroblastoma). A single intraperitoneal injection of methyl methanesulfonate caused tumors of the nervous system (oligodendroglioma, malignant neurofibroma, astrocytoma, malignant neuroinoma, mixed glioma, or meningioma of the spinal cord) in adult rats of both sexes and in the offspring of pregnant rats exposed on gestation day 15 or 21 (Clapp *et al.* 1968, IARC 1974).

Since methyl methanesulfonate was listed in the *Sixth Annual Report on Carcinogens*, additional studies in rodents have been identified. In female mice, subcutaneous injection of methyl methanesulfonate caused cancer at the injection site (sarcoma) (Segal *et al.* 1987). In male rats exposed to methyl methanesulfonate by inhalation for six weeks and then observed for life, the incidence of nasal tumors (mainly squamous-cell carcinoma) was significantly increased (IARC 1999).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to methyl methanesulfonate.

Properties

Methyl methanesulfonate is an ester of sulfuric acid that exists as a colorless to amber liquid at room temperature. It is soluble in water, dimethyl formamide, and propylene glycol, but only slightly soluble in nonpolar solvents. Methyl methanesulfonate is stable under normal temperatures and pressures, but it forms irritating corrosive compounds or toxic gases in the presence of fire (IARC 1974, Akron 2009). Physical and chemical properties of methyl methanesulfonate are listed in the following table.

Property	Information
Molecular weight	110.1 ^a
Specific gravity	1.2943 at 20°C/4°C ^a
Melting point	20°C ^a
Boiling point	203°C at 753 mm Hg ^a
Log <i>K</i> _{ow}	-0.66 ^b
Water solubility	1,000 g/L at 25°C ^b
Vapor pressure	0.31 mm Hg at 25°C ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Methyl methanesulfonate is used experimentally as a research chemical and as a solvent catalyst in polymerization, alkylation, and esterification reactions (IARC 1974, Wyatt and Pittman 2006, NIH 2007). It has been tested as a cancer chemotherapeutic agent, and the monoesters of methanesulfonic acid were considered for possible use as a reversible insect and mammalian pest chemosterilant and as a human male contraceptive (IARC 1974).

Production

Production of methyl methanesulfonate is limited, because it is used only in research (IARC 1974, 1999). Methyl methanesulfonate is not produced commercially in the United States (IARC 1999, HSDB 2009). In 2009, methyl methanesulfonate was available from 21 suppliers worldwide, including 13 U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports of methyl methanesulfonate were found.

Exposure

Exposure to methyl methanesulfonate appears to be limited to laboratory research personnel (IARC 1974, 1999). If released to air, methyl methanesulfonate will exist in the vapor phase and will react slowly with hydroxyl radicals, with a half-life of 69 days. If released to a moist environment, it will hydrolyze with a half-life of 4.56 hours at 25°C. It is not expected to bioconcentrate in aquatic organisms or volatilize from water (HSDB 2009).

Regulations

Environmental Protection Agency (EPA)

Resource Conservation and Recovery Act

Listed as a hazardous constituent of waste.

References

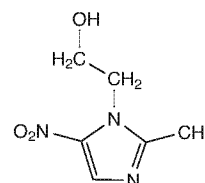
- Akron. 2009. *The Chemical Database*. The Department of Chemistry at the University of Akron. <http://ull.chemistry.uakron.edu/erd> and search on CAS number. Last accessed: 5/19/09.
- ChemIDplus. 2009. *ChemIDplus Advanced*. National Library of Medicine. <http://chem.sis.nlm.nih.gov/chemidplus/chemidheavy.jsp> and select Registry Number and search on CAS number. Last accessed: 5/19/09.
- ChemSources. 2009. *Chem Sources - Chemical Search*. Chemical Sources International. <http://www.chemsources.com/chemonline.html> and search on methyl methanesulfonate. Last accessed: 5/19/09.
- Clapp NK, Craig AW, Toya RE Sr. 1968. Oncogenicity by methyl methanesulfonate in male RF mice. *Science* 161: 160-161.
- HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number. Last accessed: 5/19/09.
- IARC. 1974. Methyl methanesulfonate. In *Some Anti-thyroid and Related Substances, Nitrofurans and Industrial Chemicals*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 7. Lyon, France: International Agency for Research on Cancer. pp. 253-260.
- IARC. 1999. Methyl methanesulfonate. In *Re-evaluation of Some Organic Chemicals, Hydrazine, and Hydrogen Peroxide*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 71. Lyon, France: International Agency for Research on Cancer. pp. 1059-1078.
- Segal A, Seidman I, Melchionne S. 1987. Induction of thymic lymphomas and squamous cell carcinomas following topical application of isopropyl methanesulfonate to female Hsd:(ICR)BR mice. *Cancer Res* 47(13): 3402-3405.
- Wyatt MD, Pittman DL. 2006. Methylating agents and DNA repair responses: Methylated bases and sources of strand breaks. *Chem Res Toxicol* 19(12): 1580-1594.

Metronidazole

CAS No. 443-48-1

Reasonably anticipated to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)



Carcinogenicity

Metronidazole is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to metronidazole caused tumors at several different tissue sites in mice and rats. Dietary administration of metronidazole caused benign and malignant lung tumors (adenoma, adenocarcinoma, and carcinoma) in mice of both sexes, lymphoma in female mice (Rustia and Shubik 1972, IARC 1977), liver cancer (hepatocellular carcinoma) and mammary-gland tumors (fibroadenoma) in female rats, and tumors of the pituitary gland (adenoma) and testes (Leydig-cell tumors) in male rats (IARC 1982).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to metronidazole. An excess of cancer of the uterine cervix was found in two epidemiological studies of women treated with metronidazole for vaginal trichomoniasis (Beard *et al.* 1979, Friedman and Ury 1980, IARC 1982); however, trichomoniasis is a risk factor for cervical cancer, and one of the studies (Beard *et al.* 1979) showed a greater excess of cancer among women with trichomoniasis who were not exposed to metronidazole. The study by Beard *et al.*, but not that by Friedman *et al.*, reported an excess of lung cancer, which may have been due to smoking.

Since metronidazole was listed in the *Fourth Annual Report on Carcinogens*, additional epidemiological studies have been identified. In a follow-up of the cohort study by Beard *et al.*, the incidence of lung cancer (bronchogenic carcinoma) was significantly increased in women exposed to metronidazole, and the excess remained after an attempt to adjust for smoking (Beard *et al.* 1988). In a study of over 12,000 people who had used metronidazole, no excess of cancer (all tissue sites combined) was found after two and a half years of follow-up (IARC 1987). A large cohort study of cancer in children prenatally exposed to metronidazole found no overall excess of cancer (all tissue sites combined); a twofold increase in the risk of neuroblastoma (cancer of the sympathetic nervous system) was not statistically significant (Thapa *et al.* 1998).

Properties

Metronidazole is a nitroimidazole compound that exists at room temperature as white to pale-yellow crystals with a slight odor (Akron 2009). It is soluble in water, ethanol, ether, chloroform, and dilute acids and sparingly soluble in dimethylformamide (IARC 1977). It is stable under normal temperatures and pressure, but may discolor

upon exposure to light (Akron 2009). Physical and chemical properties of metronidazole are listed in the following table.

Property	Information
Molecular weight	171.2 ^a
Melting point	158°C to 160°C ^a
Log <i>K</i> _{ow}	-0.02 at 25°C ^a
Water solubility	10 g/L at 25°C ^b
Vapor pressure	3.05 × 10 ⁻⁷ mm Hg at 25°C ^c

Sources: ^aHSDB 2009, ^bIARC 1977, ^cChemIDplus 2009.

Use

Metronidazole is used primarily as a drug for the treatment of infections by the parasitic protozoans *Entamoeba histolytica*, *Trichomonas vaginalis*, and *Giardia lamblia* (IARC 1977). It has also been used to treat Vincent's infection (trench mouth) and acne rosacea. It has been prescribed for invasive intestinal amoebiasis and amoebic hepatic abscess, antibiotic-associated colitis, balantidiasis, dental infection, gastritis or ulcer due to *Helicobacter pylori*, and inflammatory bowel disease (MedlinePlus 2009). It is also used as a trichomonacidal agent in veterinary medicine (IARC 1977, MedlinePlus 2009). Metronidazole may be administered orally (in capsules or tablets), vaginally (in creams, gels, or tablets), topically (in gels, creams, or lotions), or by intravenous injection (MedlinePlus 2009).

Production

Commercial production of metronidazole in the United States was first reported in 1963 (IARC 1977). In 1974, only one U.S. company reported producing metronidazole. In 1977, annual U.S. sales of metronidazole for medical use were estimated to be less than 28,600 lb. In 2009, metronidazole was available from 18 U.S. suppliers (Chem Sources 2009), and 42 drug products registered with the U.S. Food and Drug Administration contained metronidazole as an active ingredient (FDA 2009). No more recent data on U.S. production, imports, or exports were found.

Exposure

The primary routes of human exposure to metronidazole are ingestion, injection, or topical (including intravaginal) application for treatment of certain infectious diseases (MedlinePlus 2009). For treatment of bacterial infections, a recommended regimen is oral administration of 525 mg every 6 hours for seven days. As a systemic trichomonacidal agent, metronidazole typically is administered orally at a dosage of either 250 mg three times a day for seven days or 1 to 2 g twice on one day. When used to treat giardiasis, it is administered at 500 to 750 mg daily for five to ten days. For intravenous administration to treat bacterial infections, the typical regimen is 15 mg/kg of body weight initially, followed by 7.5 mg/kg every 6 hours for seven days. When administered prophylactically for colon surgery, metronidazole is injected 1 hour before surgery and at 6 and 12 hours after the first dose. When administered as a topical cream, it is usually applied twice a day for nine weeks. Metronidazole is also applied intravaginally either at 37.5 mg twice a day for five days for bacterial infections or 500 mg daily for 10 to 20 days for bacterial infections or trichomoniasis. In 2009, 149 clinical trials involving metronidazole were in progress or recently completed (ClinicalTrials 2009). Occupational exposure to metronidazole could occur through inhalation or dermal contact by workers involved in its manufacture, formulation, packaging, or administration.

Regulations

Consumer Product Safety Commission (CPSC)

Any orally administered prescription drug for human use requires child-resistant packaging.

Food and Drug Administration (FDA)

Metronidazole is a prescription drug subject to labeling and other requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

References

- Akron. 2009. *The Chemical Database*. The Department of Chemistry at the University of Akron. <http://uakron.edu/chem/erd> and search on CAS number. Last accessed: 5/09.
- Beard CM, Noller KL, O'Fallon WM, Kurland LT, Dockerty MB. 1979. Lack of evidence for cancer due to use of metronidazole. *N Engl J Med* 301(10): 519-522.
- Beard CM, Noller KL, O'Fallon WM, Kurland LT, Dahlin DC. 1988. Cancer after exposure to metronidazole. *Mayo Clin Proc* 63(2): 147-153.
- ChemIDplus. 2009. *ChemIDplus Advanced*. National Library of Medicine. <http://chem.sis.nlm.nih.gov/chemidplus/chemidheavy.jsp> and select Registry Number and search on CAS number. Last accessed: 5/09.
- ChemSources. 2009. *Chem Sources - Chemical Search*. Chemical Sources International. <http://www.chemsources.com/chemonline.html> and search on metronidazole. Last accessed: 5/09.
- ClinicalTrials. 2009. *Metronidazole*. National Institutes of Health. <http://clinicaltrials.gov/ct2/results?term=metronidazole&pg=1>. Last accessed: 5/09.
- FDA. 2009. *The Electronic Orange Book*. U.S. Food and Drug Administration. <http://www.fda.gov/cder/ob/default.htm> and select Search by Active Ingredient and search on metronidazole. Last accessed: 5/09.
- Friedman GD, Ury HK. 1980. Initial screening for carcinogenicity of commonly used drugs. *J Natl Cancer Inst* 65(4): 723-733.
- HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number. Last accessed: 5/09.
- IARC. 1977. *Metronidazole*. In *Some Miscellaneous Pharmaceutical Substances*. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, vol. 13. Lyon, France: International Agency for Research on Cancer. pp. 113-122.
- IARC. 1982. *Metronidazole*. In *Chemicals, Industrial Processes and Industries Associated with Cancer in Humans: IARC Monographs, Volumes 1 to 29*. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, suppl. 4. Lyon, France: International Agency for Research on Cancer. pp. 160-162.
- IARC. 1987. *Metronidazole*. In *Overall Evaluations of Carcinogenicity*. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, suppl. 7. Lyon, France: International Agency for Research on Cancer. pp. 250-252.
- MedlinePlus. 2009. *Metronidazole Injection*. National Library of Medicine. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601159.html>. Last accessed: 5/09.
- Rustia M, Shubik P. 1972. Induction of lung tumors and malignant lymphomas in mice by metronidazole. *J. Natl Cancer Inst* 48: 721-729.
- Thapa PB, Whitlock JA, Brockman Worrell KG, Gideon P, Mitchell EF Jr, Roberson P, Pais R, Ray WA. 1998. Prenatal exposure to metronidazole and risk of childhood cancer: A retrospective cohort study of children younger than 5 years. *Cancer* 83(7): 1461-1468.

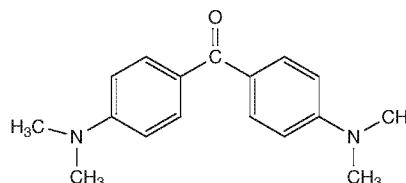
Michler's Ketone

CAS No. 90-94-8

Reasonably anticipated to be a human carcinogen

First listed in the *Third Annual Report on Carcinogens* (1983)

Also known as 4,4'-(dimethylamino)benzophenone



Carcinogenicity

Michler's ketone is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to Michler's ketone caused tumors in two rodent species and at two different tissue sites. Dietary administration of Michler's ketone caused liver cancer (hepatocellular carcinoma) in female mice and in rats of both sexes and blood-vessel cancer (hemangiosarcoma) in male mice (NCI 1979).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to Michler's ketone.

Properties

Michler's ketone is a derivative of dimethylaniline and exists as white to green crystalline leaflets or blue powder at room temperature. Michler's ketone is practically insoluble in water, very soluble in pyrimidine, soluble in alcohol and warm benzene, and very slightly soluble in ether. It is stable under normal temperatures and pressures (NCI 1979, Akron 2009, HSDB 2009). Physical and chemical properties of Michler's ketone are listed in the following table.

Property	Information
Molecular weight	268.4 ^a
Melting point	172°C ^a
Boiling point	> 360°C decomposes ^a
Log K_{ow}	3.87 ^b
Water solubility	0.4 g/L at 20°C ^b
Vapor pressure	1.07×10^{-6} mm Hg at 25°C ^b
Dissociation constant (pK_a)	12.46 ^c

Sources: ^aHSDB 2009, ^bChemIDplus 2009, ^cAkron 2009.

Use

Michler's ketone is a chemical intermediate used in the synthesis of at least 13 dyes and pigments, particularly auramine derivatives (NCI 1979, HSDB 2009). These pigments are used to make ultraviolet-cured printing ink for carton board and paper and as dyes for pen inks, carbon paper, alcoholic solvents, oils, waxes, textiles, and leather; one pigment is also used as a fungicide (Castle *et al.* 1997a,b, HSDB 2009).

Production

In 1975, U.S. production of Michler's ketone was estimated at over 908 kg (2,000 lb) (HSDB 2009). No current production data were found. In 2009, Michler's ketone was produced by one manufacturer in Europe (SRI 2009), and was available from 29 suppliers, including 16 U.S. suppliers (ChemSources 2009). U.S. imports of Michler's ketone totaled 548 kg (1,206 lb) in 1972, 20,000 kg (44,000 lb) in 1975 (HSDB 2009), and about 10,900 kg (24,000 lb) in 1983 (USITC 1984). No more recent data on U.S. imports or exports were found.

Exposure

The routes of potential human exposure to Michler's ketone are inhalation, ingestion, and dermal contact (Akron 2009). Michler's ketone may be present in some dyes used for printing and in minute quantities in final consumer products (Ozaki *et al.* 2004). Michler's ketone was measured in recycled paper and paperboard used in food packaging in Japan at concentrations of up to 12 µg/g. It was not detected in tested virgin paper or paperboard products. In another study, Michler's ketone was not detected in food that had been in contact with packaging containing Michler's ketone at a concentration of 3.9 µg/g (the highest concentration found in tested packaging) (Castle *et al.* 1997a). The U.S. Environmental Protection Agency's Toxics Release Inventory reported environmental releases of Michler's ketone of 1,100 lb in 1988 and 1,577 lb in 1995. In 1999, two indus-

trial facilities released 869 lb (TRI 2009). No release data have been reported since 1999.

The potential for occupational exposure is greatest for workers in facilities that manufacture Michler's ketone or any of the dyestuffs for which it is an intermediate (NCI 1979). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 2,026 workers, including 405 women, potentially were exposed to Michler's ketone (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

References

- Akron. 2009. *The Chemical Database*. The Department of Chemistry at the University of Akron. <http://uakron.edu/chem/erd> and search on CAS number. Last accessed: 5/19/09.
- Castle L, Damant AP, Honeybone CA, Johns SM, Jickells SM, Sharman M, Gilbert J. 1997a. Migration studies from paper and board food packaging materials. Part 2. Survey for residues of dialkylamino benzophenone UV-cure ink photoinitiators. *Food Addit Contam* 14(1): 45-52.
- Castle L, Offen CP, Baxter MJ, Gilbert J. 1997b. Migration studies from paper and board food packaging materials. 1. Compositional analysis. *Food Addit Contam* 14(1): 35-44.
- ChemIDplus. 2009. *ChemIDplus Advanced*. National Library of Medicine. <http://chem.sis.nlm.nih.gov/chemidplus/chemidheavy.jsp> and select Registry Number and search on CAS number. Last accessed: 5/19/09.
- ChemSources. 2009. *Chem Sources - Chemical Search*. Chemical Sources International. <http://www.chemsources.com/chemonline.html> and search on bisdimethylaminobenzophenone. Last accessed: 5/19/09.
- HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number. Last accessed: 5/19/09.
- NCI. 1979. *Bioassay of Michler's Ketone for Possible Carcinogenicity*. NCI Technical Report Series no. 181. DHEW (NIH) Publication No. 79-1737. Bethesda, MD: National Institutes of Health. 106 pp.
- NIOSH. 1990. *National Occupational Exposure Survey (1981-83)*. National Institute for Occupational Safety and Health. Last updated: 7/1/90. <http://www.cdc.gov/noes/noes1/x1044sic.html>.
- Ozaki A, Yamaguchi Y, Fujita T, Kuroda K, Endo G. 2004. Chemical analysis and genotoxicological safety assessment of paper and paperboard used for food packaging. *Food Chem Toxicol* 42(8): 1323-1337.
- SRI. 2009. *Directory of Chemical Producers*. Menlo Park, CA: SRI Consulting. Database edition. Last accessed: 5/19/09.
- TRI. 2009. *TRI Explorer Chemical Report*. U.S. Environmental Protection Agency. <http://www.epa.gov/triexplorer> and select 4,4'-Bis(dimethylamino)benzophenone. Last accessed: 5/19/09.
- USITC. 1984. *Imports of Benzenoid Chemicals and Products, 1983*. USITC Publication No. 1548. Washington, DC: U.S. International Trade Commission.

Mineral Oils: Untreated and Mildly Treated

CAS No.: none assigned

Known to be human carcinogens

First listed in the *First Annual Report on Carcinogens* (1980)

Carcinogenicity

Untreated and mildly treated mineral oils are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

The carcinogenicity of exposure to untreated and mildly treated mineral oils has been evaluated in numerous studies in a variety of occupations, including metal working, jute processing, mulespinning, newspaper press operation, and other newspaper work. Exposure to mineral oils was consistently and strongly associated with an increased risk of cancer of the scrotum and skin (squamous-cell carcinoma) for many occupations, including metal worker, mulespinner, and jute processor. An analysis of a series of 344 cases of scrotal cancer occurring from 1936 to 1976 in the West Midlands region of Eng-

land reported that 62% of the men had been exposed to mineral oils. Epidemiological studies (case-control, cohort, and proportional mortality studies) in metal workers have reported excesses of gastrointestinal, sinonasal, and bladder cancer, in addition to skin and scrotal cancer. Some but not all studies (case-control, cohort, and proportional mortality studies) of workers in the printing industry have reported significantly increased incidences of death from cancer of the lung, rectum, buccal cavity, and pharynx. The International Agency for Research on Cancer concluded that there was sufficient evidence for the carcinogenicity of untreated and mildly treated mineral oils in humans (IARC 1984, 1987).

Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of some untreated and mildly treated mineral oils from studies in experimental animals. Evaluation of the carcinogenicity of mineral oils in experimental animals has mainly involved experiments in which petroleum-derived base oils and formulated products were applied repeatedly to the skin of mice; however, some types of mineral oil preparations were studied in other species and by other routes of exposure. Vacuum-distillate fractions, acid-treated oils, mildly solvent-refined oils, mildly treated hydrotreated oils, aromatic oils (including solvent extracts and high-boiling-point fractions of catalytically cracked oils), and some cutting oils caused skin tumors in mice. High-boiling-point fractions of cracked oils also caused skin tumors in rabbits and monkeys (IARC 1984, 1987).

Properties

Mineral oils include lubricant base oils and products derived from them. The physical properties of lubricant oils vary widely, but generally are defined by crude oil source, carbon number distribution, boiling range, and viscosity. Mineral oils, which are refined from petroleum crude oils, are complex mixtures of straight- and branched-chain paraffinic, naphthenic, and aromatic hydrocarbons with 15 or more carbons and boiling points in the range of 300°C to 600°C; boiling points of up to 815°C have been reported for heavier oils. The viscosity of lubricant oils is described as “light” or “heavy” depending upon whether the maximum viscosity at 37.8°C is less than or equal to 20.5 mm²/sec (centistokes). The density of mineral oils at 15°C ranges from 0.820 kg/L for light paraffinic base and process oils to just over 1.0 kg/L for high aromatic base and process oils. The complete description of a mineral oil must include the nature of the final treatment step, which determines whether the material is mildly or severely treated during the refining process. Medicinal white mineral oils, which are pharmaceutical- and food-grade materials, are highly refined and free of all aromatic and unsaturated compounds. As highly refined oils, these products are not covered under this listing (IARC 1984).

Mineral oils are insoluble in water and alcohol, but soluble in benzene, chloroform, ether, carbon disulfide, and petroleum ether. Paraffinic crude oils are characterized by high wax content, high natural viscosity index (the rate of change of viscosity over a given temperature range), and relatively low aromatic hydrocarbon content. Naphthenic crude oils are generally low in wax content and relatively high in cycloparaffins and aromatic hydrocarbons. All crude oils contain some polycyclic aromatic hydrocarbons, and the proportions and types of these compounds in finished base oils are determined primarily by the refining processes (IARC 1984). Mineral oils generally do not present a fire hazard and must be preheated before ignition will occur (HSDB 2009).

Use

Mineral oils are used primarily as lubricant base oils to produce further refined oil products, including engine oils, automotive and industrial gear oils, transmission fluids, hydraulic fluids, circulating and hydraulic oils, bearing oils, machine oils, machine-tool oils, compressor and refrigerator oils, steam-engine oils, textile machine oils, air-tool oils, metalworking oils (cutting oils, roll oils, can-forming oils, and drawing oils), rust-preventative oils, heat-treating oils, transformer oils, greases, medicinal and technical-grade white oils, and processing oils (product extenders, processing aids, carriers and diluents, water repellents, surface-active agents, batching oils, mold-release oils, and wash oils). These oils are used in manufacturing (78.5% of the oils produced), mining (5.0%), construction (1.8%), and miscellaneous industries (14.7%). About 57% of the lubricating oils produced are used by the automotive industry, and the remaining 43% by other industries. In the automotive industry, lubricating oils are used as multigrade engine oils (23% of the lubricating oils produced), monograde engine oils (22%), transmission and hydraulic fluids (8%), gear oils (2%), and aviation oils (1%). In other industries, lubricating oils are used as general industrial diesel engine oils (19%), process oils (13%), metalworking oils (4%), railroad diesel engine oils (3%), and marine diesel engine oils (2%) (IARC 1984).

Production

In 1981, about 19 billion pounds of mineral oil products were used in the United States (NPRA 1981), including 16.2 billion pounds of lubricating oils, 1.5 billion pounds of waxes, 814 million pounds of aromatic oils, and 462 million pounds of greases. In 2009, mineral oils were available from 28 U.S. suppliers (ChemSources 2009). In 1984, the United States imported 17,000 kg (37,000 lb) and exported 75,000 kg (165,000 lb) of mineral oil (type not specified) (HSDB 2009).

Exposure

The primary routes of potential human exposure to mineral oils are inhalation, ingestion, and dermal contact. The major hydrocarbon constituents of lubricant base oils and derived products occur naturally in crude petroleum. The general population potentially is exposed to unused and used mineral oils that occur naturally or are present as environmental contaminants. About 2 billion liters (528 million gallons) of used lubricating oils are released into the environment every year, including 750 million liters (198 million gallons) used as road oil or in asphalt (IARC 1984).

Occupational exposure to mineral oils may occur among workers employed in the manufacture of automobiles, airplanes and parts, steel products, screws, pipes, precision parts, and transformers, as well as workers employed in brass and aluminum production, engine repair, copper mining, and newspaper and commercial printing (IARC 1984). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 1,009,473 workers, including 392,294 women, potentially were exposed to mineral oils (NIOSH 1990). The National Institute for Occupational Safety and Health reported the presence of mineral oils in the occupational environment of several plants in the 1970s. The concentration of cutting-oil mist was reported to be 0.37 to 0.55 mg/m³ for polishing of aircraft engine blades, 0.4 to 6.0 mg/m³ for machining of rough iron castings into automotive parts, 1.1 to 20 mg/m³ for manufacture of aircraft components, 0.3 to 1.3 mg/m³ for manufacture of automotive parts, from less than 0.03 to 0.8 mg/m³ for fabrication of precision metal parts, and from less than 0.035 to 3.1 mg/m³ for milling and machining operations. The concentration of transformer oil in air was re-

ported to be 0.1 to 1.4 mg/m³ for the manufacture and overhauling of large transformers (IARC 1984).

Regulations

Consumer Product Safety Commission (CPSC)

Products containing 10% or more of petroleum distillates require special labeling because of aspiration hazard.

Special packaging is required for certain household products containing 10% or more petroleum distillates and with a viscosity less than 100 Saybolt Universal seconds.

Environmental Protection Agency (EPA)

Clean Water Act

Procedures, methods, equipment, and other requirements have been established to prevent the discharge of all types of oils (including mineral oil) from all types of non-transportation-related facilities.

Products of mineral oil origin at levels that will cause interference are banned from discharge to publicly owned treatment works.

Federal Insecticide, Fungicide, and Rodenticide Act

Tolerance for residues of mineral oil on corn, grain, and sorghum = 200 ppm.

Food and Drug Administration (FDA)

Some over-the-counter drugs and products containing mineral oil must contain a warning label.

Restrictions on the use of mineral oil in food preparation and in packaging materials are prescribed in 21 CFR 172, 173, and 175-179.

When used as a lubricant with incidental food contact, mineral oil levels shall not exceed 10 ppm.

Drugs for internal use containing mineral oil must have a warning label.

Limitations on the use of mineral oil in drugs for use in animal feed are prescribed in 21 CFR 558.

Limits on the use of mineral oil as an additive in feed and drinking water of animals are prescribed in 21 CFR 573.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 5 mg/m³ for mineral-oil mist.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 5 mg/m³ for mineral-oil mist.

Threshold limit value – short term exposure limit (TLV-STEL) = 10 mg/m³ for mineral-oil mist.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 5 mg/m³ for mineral-oil mist.

Short-term exposure limit (STEL) = 10 mg/m³ for mineral-oil mist.

Immediately dangerous to life and health (IDLH) limit = 2,500 mg/m³ for mineral-oil mist.

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

References

- ChemSources. 2009. *Chem Sources - Chemical Search*. Chemical Sources International. <http://www.chemsources.com/chemonline.html> and search on mineral oil. Last accessed: 10/22/09.
- HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on mineral oil. Last accessed: 10/22/09.
- IARC. 1973. Mineral oils. In *Certain Polycyclic Aromatic Hydrocarbons and Heterocyclic Compounds*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 3. Lyon, France: International Agency for Research on Cancer. pp. 30-33.
- IARC. 1984. Mineral oils (lubricant base oils and derived products). In *Polynuclear Aromatic Compounds, Part 2. Carbon Blacks, Mineral Oils and Some Nitroarenes*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 33. Lyon, France: International Agency for Research on Cancer. pp. 87-168.
- IARC. 1987. Mineral oils: untreated and mildly-treated oils (Group 1), highly-refined oils (Group 3). In *Overall Evaluations of Carcinogenicity*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, suppl. 7. Lyon, France: International Agency for Research on Cancer. pp. 252-254.
- NIOSH. 1990. *National Occupational Exposure Survey (1981-83)*. National Institute for Occupational Safety and Health. Last updated: 7/1/90. <http://www.cdc.gov/noes/noes1/m0603sic.html>.
- NPRA. 1981. *Report on U.S. Lubricating Oil Sales*. Washington, DC: National Petroleum Refiners Association.

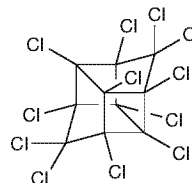
Mirex

CAS No. 2385-85-5

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as 1,1a,2,2,3,3a,4,5,5,5a,5b,6-dodecachlorooctahydro-1,3,4-metheno-1H-cyclobuta[cd]pentalene



Carcinogenicity

Mirex is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Mirex caused tumors in mice and rats by two different routes of exposure. It caused benign or malignant liver tumors after (1) administration to infant mice of both sexes by stomach tube for three weeks, followed by dietary exposure, (2) dietary administration to rats of both sexes, and (3) a single subcutaneous injection in male mice. An excess of lymphoma (reticulum-cell sarcoma) observed in male mice exposed by subcutaneous injection also may have been related to mirex exposure (IARC 1974, 1979).

Since mirex was listed in the *Second Annual Report on Carcinogens*, additional studies in rats have been identified. Dietary administration of mirex caused benign liver tumors (adenoma) in both sexes, benign tumors of the adrenal glands (pheochromocytoma) and kidney (transitional-cell papilloma) in males, and mononuclear-cell leukemia in females (NTP 1990).

Cancer Studies in Humans

The data available from epidemiological studies were inadequate to evaluate the relationship between human cancer and exposure specifically to mirex.

Properties

Mirex is a chlorinated insecticide that is an odorless snow-white crystal at room temperature (HSDB 2009). Mirex is practically insoluble in water, but is soluble in dioxane, xylene, benzene, carbon tetrachloride, and methyl ethyl ketone. It is very stable at normal temperatures and pressures (Akron 2009). Physical and chemical properties of mirex are listed in the following table.

Property	Information
Molecular weight	545.6 ^a
Melting point	485°C ^a
Log K _{ow}	5.28 ^a
Water solubility	0.085 mg/L at 25°C ^b
Vapor pressure	8 × 10 ⁻⁷ mm Hg at 25°C ^b
Vapor density relative to air	18.8 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Mirex was used in the United States from 1959 until 1972 as a fire-retardant additive and as an insecticide to control fire ants in southeastern states; the latter use continued until 1978 (IARC 1979, ATSDR

1995). From 1962 to 1976, 132 million acres in nine states were treated for fire-ant control with about 500,000 lb of mirex bait, primarily by aerial application. Mirex was also used to control other species of ants, yellow jackets, and mealy bugs in pineapples (IARC 1979). The U.S. Environmental Protection Agency canceled all registered uses of mirex in December 1977; however, selected applications were allowed until existing stocks were exhausted in June 1978.

Production

Mirex was first synthesized in the mid 1940s, but it did not become commercially available in the United States until 1958 (IARC 1979). Technical-grade mirex was produced commercially by one company in the United States until 1967. The insecticidal baits were produced until 1975, when all registrations and the rights to produce and sell baits containing mirex were transferred to the Mississippi Department of Agriculture until the supply of mirex was exhausted. One company produced an estimated 3.3 million pounds of mirex between 1959 and 1975 and purchased an additional 1.5 million pounds from another company (ATSDR 1995). Peak production occurred from 1963 to 1968. U.S. production was 41,500 lb in 1972 and less than 1,000 lb in 1975 (HSDB 2009). Mirex is available in small quantities for laboratory use from seven U.S. suppliers and four other suppliers worldwide (ChemSources 2009). Before cancellation of its registrations for technical products, mirex was imported from Brazil; however, no data on U.S. import volumes were found (ATSDR 1995). Over 90% of the mirex produced in the United States between 1950 and 1975 was exported.

Exposure

Although mirex is no longer produced or used in the United States, it is very persistent in the environment and is highly resistant to degradation. Because mirex remains in the environment for a long time, the general population may continue to be exposed at low concentrations (ATSDR 1995). Populations with the greatest potential for exposure include those who eat fish from contaminated water bodies, reside near a former mirex manufacturing or waste-disposal site, or live in areas where mirex was extensively used to control fire ants.

Mirex has a half-life of up to 10 years in the environment. It is very soluble in fat and bioaccumulates in animals. Mirex has been found in Antarctic species, indicating that it is transported over long distances (Bustnes *et al.* 2006). It has been measured in top avian predators at both poles; however, concentrations were much higher in the Antarctic species. The one U.S. plant that manufactured mirex was located on the Niagara River upstream from Lake Ontario. It was estimated that almost 6,000 lb of mirex entered Lake Ontario from that facility. From 1977 to 1999, concentrations of mirex in salmon fillets collected from Lake Ontario declined by more than tenfold, to less than 0.1 mg/kg; the decline was attributed to clean-up of the groundwater discharge from the former manufacturing site, resulting in less mirex available in Lake Ontario for biomagnification in the food chain (Makarewicz *et al.* 2003). In another study, mirex was found at concentrations of up to 360 ng/g in lake trout taken near the former manufacturing site; in lake trout in the other Great Lakes, it was found at much lower concentrations or was below the limit of detection (2 ng/g) (Hickey *et al.* 2006). In Arctic Greenland populations, the daily intake of mirex increased from 0.002 µg/kg of body weight in 1976 to 0.0044 µg/kg in 2004, even though the consumption of traditional foods declined (Deutch *et al.* 2004).

Mirex has been found in the blood of numerous human populations, especially in indigenous people of northern regions (Van Oostdam *et al.* 2004). A survey of organochlorine pesticides in maternal blood found mirex at concentrations up to 12 µg/kg of serum lipids

in Arctic populations in Greenland, Canada, Alaska, Norway, Sweden, Iceland, Finland, and Russia. The blood levels of mirex in Greenland arctic populations ranged from 34.1 to 88.1 µg/kg of lipid and correlated with Inuit consumption of seal and fish (Deutch *et al.* 2004). In Arctic Canada, mirex was detected in 84% of Inuit maternal blood samples at a mean concentration of 0.07 µg/L, but in less than 45% of samples from other ethnic groups, at a median concentration of only 0.02 µg/L. However, it was detected in only 8.5% of the corresponding cord blood plasma samples from all ethnic groups, at a mean concentration of 0.01 µg/L (Butler Walker *et al.* 2003).

Mirex was found in 46% of the blood samples collected from Akwesasne Mohawk youth living along the St. Lawrence River in New York and Quebec, at a mean concentration of 0.036 ppb. Levels were somewhat higher in youths who had been breastfed as infants, but the difference was not statistically significant (Schell *et al.* 2003). In Montreal, mirex was found in the blood of ethnic Bangladeshi and Vietnamese fishermen and in majority-community sport fishers; concentrations were highest among the majority sport fishers, because they caught and ate larger fish (Kosatsky *et al.* 1999). In a study of male sport fishers in New York State, their mean blood mirex concentration was 18.4 ng/g of lipid, significantly higher than in non-consumers of sport fish (Bloom *et al.* 2005). A study in the Great Lakes also found higher blood concentrations of mirex among men and women who consumed fish than in non-consumers (Kearney *et al.* 1999). Mirex was found in 86% of the blood samples collected from pregnant women in an agricultural community in California, at a median concentration of 0.29 ng/g of lipid (Fenster *et al.* 2006). A study in southern Spain measured organochlorine pesticides in 150 placentas and detected mirex in 40% of the samples, at a mean concentration of 0.38 ng/g of placenta (Lopez-Espinosa *et al.* 2006).

Mirex was found in all adipose-tissue samples collected at autopsy from Greenlanders; the highest mean concentration, 126 µg/kg of lipid, was found in omental fat. This was lower than found in a previous study of Greenlanders, but much higher than in studies conducted in other locations (Deutch *et al.* 2006). Breast-milk concentrations of mirex also were elevated in populations of women in New York State who had eaten contaminated local fish (Greizerstein *et al.* 1999, Fitzgerald *et al.* 2001).

The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 932 workers potentially were exposed to mirex (HSDB 2009). However, occupational exposure is now limited to workers employed at hazardous-waste sites or those involved in remediation of sites contaminated with mirex (ATSDR 1995).

Regulations

Department of Transportation (DOT)

Mirex is considered a marine pollutant, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Federal Insecticide, Fungicide, and Rodenticide Act

Registrations for all uses have been canceled.

Food and Drug Administration (FDA)

Action level in the edible portion of fish = 0.1 ppm.

References

- Akron. 2009. *The Chemical Database*. The Department of Chemistry at the University of Akron. <http://ull.chemistry.uakron.edu/erd> and search on CAS number. Last accessed: 8/11/09.
- ATSDR. 1995. *Toxicological Profile for Mirex and Chlordane*. Agency for Toxic Substances and Disease Registry. <http://www.atsdr.cdc.gov/toxprofiles/tp66.pdf>.
- Bloom MS, Vena JE, Swanson MK, Moysich KB, Olson JR. 2005. Profiles of ortho-polychlorinated biphenyl congeners, dichlorodiphenyldichloroethylene, hexachlorobenzene, and mirex among male Lake Ontario sportfish consumers: The New York State Angler cohort study. *Environ Res* 97(2): 178-194.

Bustnes JO, Tveraa T, Henden JA, Varpe O, Janssen K, Skaare JU. 2006. Organochlorines in antarctic and arctic avian top predators: A comparison between the South Polar skua and two species of northern hemisphere gulls. *Environ Sci Technol* 40(8): 2826-2831.

Butler Walker J, Seddon L, McMullen E, Houseman J, Tofflemire K, Corriveau A, *et al*. 2003. Organochlorine levels in maternal and umbilical cord blood plasma in Arctic Canada. *Sci Total Environ* 302(1-3): 27-52.

ChemIDplus. 2009. *ChemIDplus Advanced*. National Library of Medicine. <http://chem.sis.nlm.nih.gov/chemidplus/chemidheavy.jsp> and select Registry Number and search on CAS number. Last accessed: 8/11/09.

ChemSources. 2009. *Chem Sources - Chemical Search*. Chemical Sources International. <http://www.chemsources.com/chemonline.html> and search on mirex. Last accessed: 8/11/09.

Deutch B, Pedersen HS, Hansen JC. 2004. Dietary composition in Greenland 2000, plasma fatty acids and persistent organic pollutants. *Sci Total Environ* 331(1-3): 177-188.

Deutch B, Dyerberg J, Pedersen HS, Asmund G, Moller P, Hansen JC. 2006. Dietary composition and contaminants in north Greenland, in the 1970s and 2004. *Sci Total Environ* 370(2-3): 372-381.

Fenster L, Eskenazi B, Anderson M, Bradman A, Harley K, Hernandez H, Hubbard A, Barr DB. 2006. Association of *in utero* organochlorine pesticide exposure and fetal growth and length of gestation in an agricultural population. *Environ Health Perspect* 114(4): 597-602.

Fitzgerald EF, Hwang SA, Deres DA, Bush B, Cook K, Worswick P. 2001. The association between local fish consumption and DDE, mirex, and HCB concentrations in the breast milk of Mohawk women at Akwesasne. *J Expo Anal Environ Epidemiol* 11(5): 381-388.

Greizerstein HB, Stinson C, Mendola P, Buck GM, Kostyniak PJ, Vena JE. 1999. Comparison of PCB congeners and pesticide levels between serum and milk from lactating women. *Environ Res* 80(3): 280-286.

Hickey JP, Batterman SA, Chernyak SM. 2006. Trends of chlorinated organic contaminants in Great Lakes trout and walleye from 1970 to 1998. *Arch Environ Contam Toxicol* 50(1): 97-110.

HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number. Last accessed: 8/11/09.

IARC. 1974. Mirex. In *Some Organochlorine Pesticides*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 5. Lyon, France: International Agency for Research on Cancer. pp. 203-210.

IARC. 1979. Mirex. In *Some Halogenated Hydrocarbons*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 20. Lyon, France: International Agency for Research on Cancer. pp. 283-301.

Kearney JP, Cole DC, Ferron LA, Weber JP. 1999. Blood PCB, *p,p'*-DDE, and mirex levels in Great Lakes fish and waterfowl consumers in two Ontario communities. *Environ Res* 80(2 Pt 2): S138-S149.

Kosatsky T, Przybysz R, Shatenstein B, Weber JP, Armstrong B. 1999. Contaminant exposure in Montrealers of Asian origin fishing the St. Lawrence River: Exploratory assessment. *Environ Res* 80(2 Pt 2): S159-S165.

Lopez-Espinosa MJ, Granada A, Carreno J, Salvatierra M, Olea-Serrano F, Olea N. 2006. Organochlorine pesticides in placentas from southern Spain and some related factors. *Placenta*: 631-638.

Makarewicz JC, Damaske E, Lewis TW, Merner M. 2003. Trend analysis reveals a recent reduction in mirex concentrations in coho (*Oncorhynchus kisutch*) and chinook (*O. tshawytscha*) salmon from Lake Ontario. *Environ Sci Technol* 37(8): 1521-1527.

NTP. 1990. *Toxicology and Carcinogenesis Studies of Mirex (1,1a,2,2,3,3a,4,5,5,5a,5b,6-Dodecachlorooctahydro-1,3,4-metheno-1H-cyclobuta[cd]pentalene) (CAS No. 2385-85-5) in F344/N Rats (Feed Studies)*. Technical Report Series no. 313. NIH Publication No. 90-2569. Research Triangle Park, NC: National Toxicology Program. 140 pp.

Schell LM, Hubicki LA, DeCaprio AP, Gallo MV, Ravenscroft J, Tarbell A, Jacobs A, David D, Worswick P. 2003. Organochlorines, lead, and mercury in Akwesasne Mohawk youth. *Environ Health Perspect* 111(7): 954-961.

Van Oostdam JC, Dewailly E, Gilman A, Hansen JC, Odland JO, Chashchin V, *et al*. 2004. Circumpolar maternal blood contaminant survey, 1994-1997 organochlorine compounds. *Sci Total Environ* 330(1-3): 55-70.

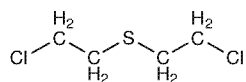
Mustard Gas

CAS No. 505-60-2

Known to be a human carcinogen

First listed in the *First Annual Report on Carcinogens* (1980)

Also known as bis(2-chloroethyl) sulfide



Carcinogenicity

Mustard gas is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

In several epidemiological studies, exposure to mustard gas (through military use or occupationally) was associated with an increased risk

of lung or other respiratory-tract cancer. Among mustard-gas production workers, the risk of respiratory cancer was higher in individuals who had been exposed to mustard gas for longer periods (IARC 1975, 1987). Since mustard gas was listed in the *First Annual Report on Carcinogens* and subsequently reviewed by IARC (1987), it has been reported to be associated with cancer at several other tissue sites. A cohort study in England found significant excesses of laryngeal, pharyngeal, upper-respiratory-tract, and lung cancer in workers employed in the manufacture of mustard gas during World War II (Easton *et al*. 1988).

Cancer Studies in Experimental Animals

Mustard gas caused cancer in mice of both sexes. When administered by inhalation or intravenous injection, it caused lung tumors, and when administered by subcutaneous injection, it caused tumors at the injection site (fibrosarcoma or sarcoma) (IARC 1975, 1987).

Studies on Mechanisms of Carcinogenesis

Mustard gas caused genetic damage in all systems in which it was tested. It caused DNA damage in bacteria and gene mutations in fungi. In *Drosophila melanogaster*, it caused dominant lethal mutations, sex-linked recessive lethal mutations, aneuploidy, and heritable translocations. In cultured rodent cells, it caused mutations, chromosomal aberrations, and DNA damage. In mice exposed by intraperitoneal injection, mustard gas was shown to bind covalently to DNA, RNA, and protein (IARC 1987).

Properties

Mustard gas is a sulfur mustard alkylating agent that exists at room temperature as a colorless to yellow oily liquid with a sweet, agreeable odor (IARC 1975). It is insoluble in water, soluble in acetone, benzene, ethanol, ether, and other common organic solvents, miscible in petroleum ether, and highly soluble in lipids. It hydrolyzes readily in aqueous solution (Akron 2009). Physical and chemical properties of mustard gas are listed in the following table.

Property	Information
Molecular weight	159.1 ^a
Specific gravity	1.2741 at 20°C/4°C (liquid) 1.338 at 13°C (solid) ^a
Melting point	13°C to 14°C ^a
Boiling point	215°C to 217°C ^a
Log <i>K</i> _{ow}	2.41 ^b
Water solubility	0.000684 g/L at 25°C ^a
Vapor pressure	0.11 mm Hg at 25°C ^a
Vapor density relative to air	5.4 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Mustard gas is a vesicant (blister-inducing agent) first used in chemical warfare in World War I. It was also used in chemical warfare in Ethiopia in 1936 and in the Iran-Iraq war from 1984 to 1988. Small amounts are used in research as a model compound in biological studies of alkylating agents. Mustard gas was tested as an anticancer agent, but its clinical use was not successful because of its high toxicity (IARC 1975, ATSDR 2003).

Production

By the end of World War I, daily U.S. production of mustard gas had reached about 18,000 kg (40,000 lb). The United States continued to produce and stockpile mustard-gas chemical weapons until 1968, accumulating more than 34 million pounds (ATSDR 2003). The United States no longer produces, imports, or exports mustard gas

and signed the International Chemical Weapons Convention treaty in 1997, which mandated destruction of all chemical weapons by 2007 (CDC 2010). In 2009, mustard gas was available in research quantities from U.S. supplier (ChemSources 2009).

Exposure

The primary routes of potential human exposure to mustard gas are inhalation and dermal contact; however, the general population typically is not exposed to mustard gas. Aging stockpiles of mustard gas are stored at eight U.S. Army bases and are scheduled for destruction. Although the greatest risk of exposure to date has been among military personnel, there is some small risk of exposure for people living near military installations where mustard gas is stockpiled and destroyed or in the event of accidental releases or a chemical-warfare attack. People may also be exposed to residues of mustard gas disposed of in bulk quantities years or even decades ago if these disposal sites are disturbed (ATSDR 2003, HSDB 2009).

Bullman and Kang (1994) reviewed the effects of mustard gas and other hazards on U.S. military personnel. During World War I, as many as 28,000 of the American Expeditionary Forces were exposed to mustard gas, but seldom to lethal concentrations, because the gas was dispersed on the battlefield. Although mustard gas was not used in World War II, the United States produced and stockpiled it for possible use and conducted research to prepare for the threat of chemical-warfare attack. Top-secret experiments to test protective equipment, clothing, and antivesicant ointments, involving patch or drop tests, chamber tests, and field tests, were conducted with military volunteers. In the patch or drop tests, which assessed the strength of protective ointments, 15,000 to 60,000 soldiers and sailors were exposed to mustard gas. In chamber tests, protective masks and clothing were evaluated by exposure of volunteers to the chemical in a gas chamber for an hour or more every day or every other day until penetration was observed, evidenced by moderate to intense chemical burns on the skin. The same outcome was sought in field tests of the quality of masks, protective clothing, and ointments, which required soldiers to cross tropical or subtropical lands where the gas was dropped. In chamber and field tests, at least 4,000 servicemen were exposed to mustard gas.

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act

Threshold planning quantity (TPQ) = 500 lb.

Reportable quantity (RQ) = 500 lb.

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed as a hazardous constituent of waste.

References

Akron. 2009. *The Chemical Database*. The Department of Chemistry at the University of Akron. <http://uakron.edu/chem/erd> and search on CAS number. Last accessed: 11/22/09.

ATSDR. 2003. *Toxicological Profile for Sulfur Mustard (Update)*. Agency for Toxic Substances and Disease Registry. <http://www.atsdr.cdc.gov/toxprofiles/tp49.pdf>.

Bullman TA, Kang HK. 1994. The effects of mustard gas, ionizing radiation, herbicides, trauma, and oil smoke on US military personnel: the results of veteran studies. *Annu Rev Public Health* 15: 69-90.

CDC. 2010. *Overview of U.S. Chemical Weapons Elimination*. Centers for Disease Control and Prevention. <http://www.cdc.gov/nceh/demil/overview.htm>. Last accessed: 3/3/10.

ChemIDplus. 2009. *ChemIDplus Advanced*. National Library of Medicine. <http://chem.sis.nlm.nih.gov/chemidplus/chemidheavy.jsp> and select Registry Number and search on CAS number. Last accessed: 10/22/09.

ChemSources. 2009. *Chem Sources - Chemical Search*. Chemical Sources International. <http://www.chemsources.com/chemonline.html> and search on chloroethyl sulfide. Last accessed: 10/22/09.

Easton DF, Peto J, Doll R. 1988. Cancers of the respiratory tract in mustard gas workers. *Br J Ind Med* 45(10): 652-659.

HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number. Last accessed: 10/22/09.

IARC. 1975. Mustard gas. In *Some Aziridines, N-, S-, and O-Mustards and Selenium*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 9. Lyon, France: International Agency for Research on Cancer. pp. 181-192.

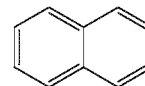
IARC. 1987. Mustard gas. In *Overall Evaluations of Carcinogenicity*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, suppl. 7. Lyon, France: International Agency for Research on Cancer. pp. 259-260.

Naphthalene

CAS No. 91-20-3

Reasonably anticipated to be a human carcinogen

First listed in the *Eleventh Report on Carcinogens* (2004)



Carcinogenicity

Naphthalene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure of rats to naphthalene by inhalation caused nasal tumors, which are rare in this species. Two types of nasal tumor were observed: olfactory epithelial neuroblastoma of the nose, which is a highly malignant and extremely rare tumor of the lining of the nose, and respiratory epithelial adenoma, which also is rare (NTP 2000). At the time the National Toxicology Program study was published, neither type of tumor had been observed in the historical controls (299 males and females) in NTP two-year studies that used the same feed as the naphthalene bioassay. (As of 2010, no nasal tumors had been observed in 1,297 male or 1,247 female controls.) The incidence of neuroblastoma of the olfactory epithelium increased with increasing exposure level in both sexes and was significantly increased at the highest exposure level in females. Some of the neuroblastomas also invaded the brain. The incidence of respiratory epithelial adenoma was significantly increased in males, but not in females. In female B6C3F₁ mice, inhalation exposure to naphthalene caused lung tumors (NTP 1992). The International Agency for Research on Cancer (2002) concluded that there was sufficient evidence for the carcinogenicity of naphthalene in experimental animals.

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to naphthalene. Two case-series studies of cancer in individuals exposed to naphthalene were identified; the first study reported cancer of the larynx and at other tissue sites among German workers occupationally exposed to naphthalene, and the second reported colorectal cancer among Africans who had used a naphthalene compound for medicinal purposes (Ajao *et al.* 1988, NTP 2002).

Studies on Mechanisms of Carcinogenesis

Naphthalene caused mutations in insects, but not in bacteria or cultured human lymphoblastoid cells (Sasaki *et al.* 1997, Grosovsky *et al.* 1999, NTP 2002). It caused other types of genetic damage in some but not all test systems. In newt larvae, naphthalene induced micronucleus formation. In cultured mammalian cells, it caused chromosomal aberrations, sister chromatid exchange, and formation of kinetochore-negative micronuclei, but did not cause DNA strand

breaks, formation of kinetochore-positive micronuclei, or cell transformation. Inhalation exposure of rats to naphthalene caused oxidative stress and DNA damage in liver and brain tissue (IARC 2002, NTP 2002).

When administered to experimental animals dermally, orally, or by inhalation, naphthalene is rapidly absorbed and metabolized (NTP 2000). Evidence suggesting that naphthalene is absorbed in humans comes from studies of workers in a coke plant, which found that concentrations of naphthalene metabolites in the urine were significantly correlated with concentrations of naphthalene in personal air samples (Bieniek 1994, 1997). The first step in the metabolism of naphthalene is formation of naphthalene-1,2-oxide (as two stereoisomers, 1*R*,2*S*-oxide and 1*S*,2*R*-oxide) through the action of cytochrome P450 enzymes in the presence of the coenzyme NADPH. These oxides are metabolized further by three pathways: (1) hydration by epoxide hydrolases into dihydrodiols, (2) conjugation by glutathione transferases, and (3) spontaneous rearrangement into 1-naphthol and 2-naphthol, which are converted to naphthoquinones (Chichester *et al.* 1994, Shultz *et al.* 1999). Naphthalene is excreted in the urine as the unchanged parent compound or as metabolites, including 1-naphthol, 2-naphthol, naphthoquinones, dihydroxynaphthalenes, and conjugated forms, including glutathione, cysteine, glucuronic acid, and sulfate conjugates (NTP 2002).

The mechanism by which naphthalene causes cancer is unknown. A strong correlation has been observed between the rates of formation of the stereoisomer (1*R*,2*S*)-naphthalene oxide in various tissues and the selective toxicity of naphthalene to these tissues, suggesting that this metabolite may play a role in naphthalene's toxicity to the lung and other tissues (Buckpitt and Franklin 1989). Oxidative damage and DNA breakage, observed in rat liver and brain tissue, may contribute to naphthalene's toxicity and carcinogenicity.

Properties

Naphthalene is a polycyclic aromatic hydrocarbon that exists at room temperature as a white crystalline solid with an aromatic odor. It is insoluble in water but soluble in methanol, ethanol, benzene, toluene, olive oil, turpentine, chloroform, carbon tetrachloride, ether, hydro-naphthalenes, fixed and volatile oils, and ethylene dichloride. It is stable in closed containers under normal temperatures and pressures (Akron 2009). Physical and chemical properties of naphthalene are listed in the following table.

Property	Information
Molecular weight	128.2
Density	1.162 g/cm ³ at 20°C
Melting point	80.2°C
Boiling point	217.9°C
Log <i>K</i> _{ow}	3.3
Water solubility	0.031 g/L at 25°C
Vapor pressure	0.085 mm Hg at 25°C
Vapor density relative to air	4.42

Source: HSDB 2009.

Use

The principal use of naphthalene in the United States is as an intermediate in the production of phthalic anhydride, which in turn is an intermediate in the production of phthalate plasticizers, pharmaceuticals, insect repellents, and other materials. Naphthalene has also been used as an intermediate in the production of 1-naphthyl-*N*-methylcarbamate insecticides, β -naphthol, synthetic leather-tanning chemicals, surfactants (e.g., naphthalene sulfonates), moth repellents, and toilet-bowl deodorizers (ATSDR 2005, HSDB 2009). In 1999, 59% of naphthalene was used for production of phthalic an-

hydride, 21% for production of surfactant and dispersant chemicals, 11% for production of insecticides, and 9% in moth repellents and for other purposes (CMR 1999). The Naphthalene Panel of the American Chemistry Council reported in 2002 that naphthalene was no longer used directly in tanneries, in the textile industry, or in the production of toilet-bowl deodorizers and that β -naphthol was not manufactured in the United States (ACC 2002).

Production

Naphthalene is produced from either coal tar (which contains approximately 10% naphthalene), by condensation and separation of coal tar from coke-oven gases, or from petroleum, by dealkylation of methyl-naphthalenes. In the United States, most naphthalene was produced from petroleum through the 1980s. U.S. production of naphthalene peaked in 1968, at 900 million pounds, decreasing to 222 million pounds by 1994 (ATSDR 2005). In 2000, production was 235 million pounds, of which over 90% (219 million pounds) was from coal tar (CEH 2000). In 2002, estimated U.S. production capacity was 215 million pounds (ATSDR 2005). In 2009, two U.S. producers of naphthalene were identified (SRI 2009).

From 1989 to 1998, U.S. demand for naphthalene grew 0.5% per year. Demand was 246 million pounds in 1998 and 248 million pounds in 1999. Demand for naphthalene sulfonates, used primarily as superplasticizer additives to increase the flowability of concrete, grew steadily in the late 1990s (CMR 1999). In 2000, estimated consumption of naphthalene was 241 million pounds (ATSDR 2005). In 2009, naphthalene was available from 28 U.S. suppliers (ChemSources 2009). Between 1989 and 2003, U.S. imports of naphthalene ranged from a high of 18.5 million kilograms (40.9 million pounds) in 1989 to a low of 1.1 million kilograms (2.5 million pounds) in 1999. In 2008, imports totaled 8.1 million kilograms (17.9 million pounds). Between 1989 and 2008, U.S. exports of naphthalene ranged from a low of 2.5 million liters (660,000 gallons) in 1993 to a high of 64.9 million liters (17.1 million gallons) in 1998; in 2009, exports were 4.8 million liters (1.3 million gallons) (USITC 2009).

Exposure

The general population potentially is exposed to naphthalene through inhalation of ambient and indoor air. Accidental ingestion of household products containing naphthalene, mainly by children, has been reported. Dermal exposure to naphthalene may occur through handling or wearing of clothing stored with moth repellents containing naphthalene. The average daily intake of naphthalene from ambient air was estimated at 19 μ g, based on an average naphthalene concentration of 0.95 μ g/m³ in urban and suburban air and an inhalation rate of 20 m³/day (ATSDR 2005). According to the U.S. Environmental Protection Agency's Toxics Release Inventory, environmental releases of naphthalene have decreased annually since 1998, when almost 6 million pounds was released. In 2007, 983 facilities released over 2.7 million pounds of naphthalene, of which more than half was released to air (TRI 2009).

The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 112,700 workers potentially were exposed to naphthalene (NIOSH 1990). Workers identified by EPA as potentially exposed to naphthalene include beta-naphthol makers, celluloid makers, coal-tar workers, dye-chemical makers, fungicide makers, hydronaphthalene makers, moth-repellent workers, phthalic anhydride makers, smokeless-powder makers, tannery workers, textile-chemical workers, and aluminum reduction plant workers (EPA 1980). No more recent occupational exposure surveys were found. However, industry estimates in 2002 indicated that about 1,000 workers were employed by the largest U.S. tar-distillation and wood-preservation

company and that fewer than 50 workers in the moth-repellent industry potentially were exposed to naphthalene (ACC 2002). These estimates did not include workers potentially exposed to naphthalene in production of phthalic anhydride and other uses. Workplace air concentrations of naphthalene have been measured in many studies and vary by industry. In the vulcanization step of tire manufacturing, naphthalene was measured at concentrations of up to 1.09 mg/m³, resulting in an estimated daily intake of 0.0029 mg/kg of body weight (Durmusoglu 2007). A survey by the National Institute for Occupational Safety and Health in 1980 reported air concentrations of naphthalene as high as 10.2 µg/m³ in an area sample and 19.3 µg/m³ in a personal sample (ATSDR 2005).

Regulations

Department of Transportation (DOT)

Naphthalene is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

Mobile Source Air Toxics: Listed as a substance for which regulations are to be developed.

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Clean Water Act

Effluent Guidelines: Listed as a toxic pollutant.

Designated a hazardous substance.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of naphthalene = U165, F024, F025, F034, K001, K035, K087, K145.

Listed as a hazardous constituent of waste.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 10 ppm (50 mg/m³).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 10 ppm (50 mg/m³).

Threshold limit value – short-term exposure limit (TLV-STEL) = 15 ppm (75 mg/m³).

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 10 ppm (50 mg/m³).

Short-term exposure limit (STEL) = 15 ppm (75 mg/m³).

Immediately dangerous to life and health (IDLH) limit = 250 ppm (1,250 mg/m³).

References

- ACC. 2002. Price CM, American Chemical Council, Arlington, VA, letter to Jameson CW, National Toxicology Program, Research Triangle Park, NC, 10/2/2002.
- Ajao OG, Adenuga MO, Ladipo JK. 1988. Colorectal carcinoma in patients under the age of 30 years: A review of 11 cases. *JR Coll Surg Edinb* 33(5): 277-279.
- Akron. 2009. *The Chemical Database*. The Department of Chemistry at the University of Akron. <http://ull.chemistry.uakron.edu/erd> and search on CAS number. Last accessed: 10/22/09.
- ATSDR. 2005. *Toxicological Profile for Naphthalene, 1-Methylnaphthalene, and 2-Methylnaphthalene*. Agency for Toxic Substances and Disease Registry. <http://www.atsdr.cdc.gov/toxprofiles/tp67.pdf>.
- Bieniek G. 1994. The presence of 1-naphthol in the urine of industrial workers exposed to naphthalene. *Occup Environ Med* 51(5): 357-359.
- Bieniek G. 1997. Urinary naphthols as an indicator of exposure to naphthalene. *Scand J Work Environ Health* 23(6): 414-420.
- Buckpitt AR, Franklin RB. 1989. Relationship of naphthalene and 2-methylnaphthalene metabolism to pulmonary bronchiolar epithelial cell necrosis. *Pharmacol Ther* 41(1-2): 393-410.
- CEH. 2000. *Chemical Economics Handbook*, vol. 27. Menlo Park, CA: SRI International.
- ChemSources. 2009. *Chem Sources - Chemical Search*. Chemical Sources International. <http://www.chemsources.com/chemonline.html> and search on naphthalene. Last accessed: 10/22/09.

Chichester CH, Buckpitt AR, Chang A, Plopper CG. 1994. Metabolism and cytotoxicity of naphthalene and its metabolites in isolated murine Clara cells. *Mol Pharmacol* 45(4): 664-672.

CMR. 2002. Chemical profile — naphthalene. *Chem Mark Rep* 5/31/99.

Durmusoglu E, Aslan S, Can E, Bulut Z. 2007. Health risk assessment of workers' exposure to organic compounds in a tire factory. *Hum Ecol Risk Assess* 13: 209-222.

EPA. 1980. *Ambient Water Quality Criteria for Naphthalene*. EPA 440-5-80-059. Washington, DC: U.S. Environmental Protection Agency.

Grososky AJ, Sasaki JC, Arey J, Eastmond DA, Parks KK, Atkinson R. 1999. Evaluation of the potential health effects of the atmospheric reaction products of polycyclic aromatic hydrocarbons. *Res Rep Health Eff Inst* 84: 1-22.

HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number. Last accessed: 8/12/09.

IARC. 2002. Naphthalene. In *Traditional Herbal Medicines, Some Mycotoxins, Naphthalene and Styrene*. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 82. Lyon, France: International Agency for Research on Cancer. pp. 367-435.

NIOSH. 1990. *National Occupational Exposure Survey (1981-83)*. National Institute for Occupational Safety and Health. Last updated 7/1/90. <http://www.cdc.gov/noes/noes1/49600sic.html>.

NTP. 1992. *Toxicology and Carcinogenesis Studies of Naphthalene (CAS No. 91-20-3) in B6C3F₁ Mice (Inhalation Studies)*. Technical Report Series no. 410. Research Triangle Park, NC: National Toxicology Program. 410 pp.

NTP. 2000. *Toxicology and Carcinogenesis Studies of Naphthalene (CAS No. 91-20-3) in F344/N Rats (Inhalation Studies)*. Technical Report Series no. 500. Research Triangle Park, NC: National Toxicology Program. 176 pp.

NTP. 2002. *Report on Carcinogens Background Document for Naphthalene*. National Toxicology Program. <http://ntp.niehs.nih.gov/ntp/newhomero/roc11/NaphthalenePub.pdf>.

Sasaki JC, Arey J, Eastmond DA, Parks KK, Grososky AJ. 1997. Genotoxicity induced in human lymphoblasts by atmospheric reaction products of naphthalene and phenanthrene. *Mutat Res* 393(1-2): 23-35.

Shultz MA, Choudary PV, Buckpitt AR. 1999. Role of murine cytochrome P-450 2F2 in metabolic activation of naphthalene and metabolism of other xenobiotics. *J Pharmacol Exp Ther* 290(1): 281-288.

SRI. 2009. *Directory of Chemical Producers*. Menlo Park, CA: SRI Consulting. Database edition. Last accessed: 10/26/09.

TRI. 2009. *TRI Explorer Chemical Report*. U.S. Environmental Protection Agency. <http://www.epa.gov/triexplorer> and select Naphthalene. Last accessed: 10/26/09.

USITC. 2009. *USITC Interactive Tariff and Trade DataWeb*. United States International Trade Commission. http://dataweb.usitc.gov/scripts/user_set.asp and search on HTS no. 270740. Last accessed: 12/29/09.

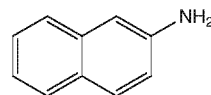
2-Naphthylamine

CAS No. 91-59-8

Known to be a human carcinogen

First listed in the *First Annual Report on Carcinogens* (1980)

Also known as β-naphthylamine



Carcinogenicity

2-Naphthylamine is known to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Epidemiological studies have shown that occupational exposure to 2-naphthylamine, either alone or present as an impurity in other compounds, causes cancer of the urinary bladder. Studies of dye-stuff workers and of chemical workers exposed mainly to 2-naphthylamine found increased risks of urinary-bladder cancer that could not be explained by workers' smoking habits. At one dyestuff plant, the cancer risk increased with increasing exposure to 2-naphthylamine. In addition, many case reports have linked 2-naphthylamine exposure with urinary-bladder cancer in workers who manufactured or used 2-naphthylamine. The International Agency for Research on Cancer concluded that there was sufficient evidence for the carcinogenicity of 2-naphthylamine in humans (IARC 1974, 1987).

Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of 2-naphthylamine from studies in experimental animals. Oral exposure to 2-naphthylamine caused urinary-bladder cancer (carcinoma) in hamsters, dogs, and rhesus monkeys and benign liver tumors (hepatocellular adenoma) in mice (IARC 1974). Since 2-naphthylamine was listed in the *First Annual Report on Carcinogens*, additional studies in rodents have been identified. Oral administration of 2-naphthylamine to rats caused a low incidence of urinary-bladder cancer (carcinoma), and administration to mice by intraperitoneal injection caused benign lung tumors (adenoma) (IARC 1987).

Studies on Mechanisms of Carcinogenesis

2-Naphthylamine caused genetic damage in various test systems, including mutations in bacteria, yeast, insects, plants, cultured human and other mammalian cells, and experimental animals exposed *in vivo*. Other types of genetic damage observed in some of these systems included DNA strand breaks, chromosomal aberrations, micronucleus formation, aneuploidy, sister chromatid exchange, and cell transformation (IARC 1987, Gene-Tox 1998).

The mechanism by which 2-naphthylamine causes cancer is thought to require its metabolism to a reactive form. When arylamines, such as 2-naphthylamine, are metabolized, they are either activated via N-hydroxylation (by cytochrome P450 liver enzymes) or detoxified via pathways such as N-acetylation. The N-hydroxylamine metabolites can form adducts with blood-serum proteins (such as hemoglobin), which circulate freely, or they can undergo further metabolism (conjugation) to form reactive compounds that can be transported to the bladder and can bind to DNA (Yu *et al.* 2002). 2-Naphthylamine DNA adducts have been found in bladder and liver cells from exposed dogs (IARC 1987).

Properties

2-Naphthylamine is an aromatic amine (arylamine) that exists at room temperature as colorless crystals with a faint aromatic odor. It is soluble in hot water, alcohol, ether, and many organic solvents. 2-Naphthylamine oxidizes in the presence of air, and the vapors can be explosive (IARC 1974, Akron 2009). Physical and chemical properties of 2-naphthylamine are listed in the following table.

Property	Information
Molecular weight	143.2
Specific gravity	1.061 at 98°C/4°C
Melting point	111°C to 113°C
Boiling point	306°C
Log K_{ow}	2.28
Water solubility	0.00640 g/L at 18°C
Vapor pressure	2.56×10^{-4} mm Hg at 25°C
Vapor density relative to air	4.95
Dissociation constant (pK_a)	4.16

Source: HSDB 2009.

Use

2-Naphthylamine now is used only in laboratory research. It formerly was used as an intermediate in the manufacture of dyes, as an antioxidant in the rubber industry, and to produce 2-chloronaphthylamine (IARC 1974, HSDB 2009).

Production

2-Naphthylamine was commercially produced in the United States from at least the early 1920s to the early 1970s. In 1955 (the last year for which production data were found), 581,000 kg (1.3 million pounds) was produced by four manufacturers (IARC 1974). Since

its commercial manufacture and use were banned in the early 1970s, 2-naphthylamine has been available only in small quantities for laboratory research. In 2009, it was available from 10 U.S. suppliers (ChemSources 2009). 2-Naphthylamine has not been imported in significant amounts since 1967, when U.S. imports totaled 17,400 kg (38,400 lb) (IARC 1974).

Exposure

Because commercial production and use of 2-naphthylamine are banned, the potential for exposure is low. The general population may be exposed through inhalation of emissions from sources where nitrogen-containing organic matter is burned, such as coal furnaces and cigarettes (HSDB 2009). The U.S. Environmental Protection Agency's Toxics Release Inventory listed one industrial facility reporting releases of 2-naphthylamine for 1998 through 2001; none was released in 1998, and releases were 8 lb in 1999, 15 lb in 2000, and 265 lb in 2001. No records of earlier releases were found (TRI 2009). Mainstream cigarette smoke from eight different U.S. conventional market cigarettes contained 2-naphthylamine at concentrations of 1.5 to 14.1 ng per cigarette (Stabbert *et al.* 2003); other investigators reported levels as high as 35 ng per cigarette (Hoffman *et al.* 1997). For sidestream smoke, a concentration of 67 ng per cigarette was reported (Patrianakos and Hoffmann 1979). 2-Naphthylamine also occurs as an impurity (0.5% or less) in commercially produced 1-naphthylamine.

At greatest risk of occupational exposure to 2-naphthylamine are laboratory technicians and scientists who use it in research. Before U.S. commercial production of 2-naphthylamine and its use in the dye and rubber industries were banned, workers in these industries potentially were exposed. The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 420 workers potentially were exposed to 2-naphthylamine (NIOSH 1976), and the National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 275 workers, including 265 women, potentially were exposed (NIOSH 1990).

Regulations

Department of Transportation (DOT)

2-Naphthylamine is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Comprehensive Environmental Response, Compensation, and Liability Act
Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of 2-naphthylamine = U168.
Listed as a hazardous constituent of waste.

Occupational Safety and Health Administration (OSHA)

Potential occupational carcinogen: Engineering controls, work practices, and personal protective equipment are required.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = exposure by all routes should be as low as possible.

National Institute for Occupational Safety and Health (NIOSH)

Listed as a potential occupational carcinogen.

References

Akron. 2009. *The Chemical Database*. The Department of Chemistry at the University of Akron. <http://uakron.edu/chem/chemdb/> and search on CAS number. Last accessed: 11/18/09.

ChemSources. 2009. *Chem Sources - Chemical Search*. Chemical Sources International. <http://www.chemsources.com/chemonline.html> and search on naphthylamine. Last accessed: 10/22/09.

Gene-Tox. 1998. *Genetic Toxicology Data Bank*. National Library of Medicine. Last updated: 4/8/98. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?GENETOX> and search on CAS number.

Hoffman D, Djordjevic M, Hoffman I. 1997. The changing cigarette. *Prev Med* 26: 427-434.

HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number. Last accessed: 10/22/09.

IARC. 1974. 2-Naphthylamine. In *Some Aromatic Amines, Hydrazine and Related Substances, N-Nitroso Compounds and Miscellaneous Alkylating Agents*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 4. Lyon, France: International Agency for Research on Cancer. pp. 97-111.

IARC. 1987. 2-Naphthylamine. In *Overall Evaluations of Carcinogenicity*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, suppl. 7. Lyon, France: International Agency for Research on Cancer. pp. 261-263.

NIOSH. 1976. *National Occupational Hazard Survey (1972-74)*. DHEW (NIOSH) Publication No. 78-114. Cincinnati, OH: National Institute for Occupational Safety and Health.

NIOSH. 1990. *National Occupational Exposure Survey (1981-83)*. National Institute for Occupational Safety and Health. Last updated 7/1/90. <http://www.cdc.gov/noes/noes1/50065sic.html>.

Patrianakos C, Hoffmann D. 1979. Chemical studies in tobacco smoke LXIV. On the analysis of aromatic amines in cigarette smoke. *J Anal Toxicol* 3: 150-154.

Stabbert R, Schafer KH, Biefel C, Rustemeier K. 2003. Analysis of aromatic amines in cigarette smoke. *Rapid Commun Mass Spectrom* 17(18): 2125-2132.

TRI. 2009. *TRI Explorer Chemical Report*. U.S. Environmental Protection Agency. Last updated: 3/19/09. <http://www.epa.gov/triexplorer> and select Beta-Naphthylamine.

Yu MC, Skipper PL, Tannenbaum SR, Chan KK, Ross RK. 2002. Arylamine exposures and bladder cancer risk. *Mutat Res* 506-507: 21-28.

Nickel Compounds and Metallic Nickel

Introduction

Nickel compounds and metallic nickel have many industrial and commercial applications, including use in stainless steel and other nickel alloys, catalysts, batteries, pigments, and ceramics. Nickel and Certain Nickel Compounds were listed in the *First Annual Report on Carcinogens* (1980) as *reasonably anticipated to be human carcinogens*. Nickel compounds as a class were first listed as *known to be human carcinogens* in the *Tenth Report on Carcinogens* (2002); this listing supersedes the listing of "certain nickel compounds" and applies to all members of the class. Metallic nickel was reevaluated in 2000 and remains listed as *reasonably anticipated to be a human carcinogen*. Nickel alloys were reviewed in 2000 but were not recommended for listing in the Report on Carcinogens (see Appendix C).

The profiles for nickel compounds and metallic nickel follow this introduction. The evidence for carcinogenicity from cancer studies in experimental animals and humans is discussed separately for nickel compounds and metallic nickel. However, most of the information on mechanisms of carcinogenesis, properties, use, production, exposure, and regulations is common to both nickel compounds and metallic nickel and therefore is combined into one section following the discussions of cancer studies.

Nickel Compounds

No separate CAS No. assigned for lead compounds as a class

Known to be human carcinogens

First listed in the *Tenth Report on Carcinogens* (2002)

Carcinogenicity

Nickel compounds are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans, including epidemiological and mechanistic studies. The combined results of epidemiological studies, mechanistic studies, and cancer studies in rodents support the concept that nickel compounds generate nickel

ions in target cells at sites critical for carcinogenesis, thus allowing consideration and evaluation of these compounds as a single group.

Cancer Studies in Humans

Several epidemiological cohort studies of workers exposed to various nickel compounds showed an elevated risk of death from lung cancer and nasal cancer. Although the precise nickel compound responsible for the carcinogenic effects in humans is not always clear, studies indicate that nickel sulfate and the combinations of nickel sulfides and oxides encountered in the nickel-refining industry cause cancer in humans. The International Agency for Research on Cancer concluded that there was sufficient evidence of the carcinogenicity of nickel compounds encountered in the nickel-refining industry in humans (IARC 1990). In an additional study, nickel-refinery workers exposed primarily to soluble nickel compounds had a significant excess risk of lung cancer, and smoking and nickel exposure had a synergistic effect on cancer risk (Anderson *et al.* 1996). These workers also had an excess risk of nasal cancer.

Cancer Studies in Experimental Animals

In rats and in some studies with mice, inhalation or intratracheal instillation of nickel subsulfide or nickel oxide led to dose-related induction of benign and malignant lung tumors, including carcinoma (IARC 1990, NTP 1996a,b). Inhalation of nickel compounds also caused tumors at tissue sites other than the lung; in particular, benign or malignant adrenal-gland tumors (pheochromocytoma) were observed in rats (NTP 1996a,b). Injection of rodents with various nickel compounds was repeatedly shown to cause dose-dependent increases in tumors in several species and at several different sites. Subcutaneous, intramuscular, intraperitoneal, subperiosteal, intrafemoral, intrapleural, intracerebral, intrarenal, intratesticular, and intraocular injections of nickel compounds all caused cancer (usually sarcoma) at the injection site. Injection of nickel also produced distant tumors of the liver in some strains of mice. IARC concluded that there was sufficient evidence of the carcinogenicity of several nickel compounds (monoxides, hydroxides, and crystalline sulfides) in experimental animals (IARC 1990).

Soluble nickel acetate is a complete transplacental carcinogen in rats. Brief exposure of pregnant rats to nickel acetate by intraperitoneal injection during pregnancy caused pituitary cancer in the offspring. Transplacental exposure to nickel acetate followed by exposure of the offspring to barbital (a known tumor promoter) caused kidney tumors (renal cortical and pelvic tumors) (Diwan *et al.* 1992). In adult rats, injection of soluble nickel salts followed by barbital exposure caused kidney cancer (renal cortical adenocarcinoma) that frequently metastasized to the lung, liver, and spleen (Kasprzak *et al.* 1990).

Metallic Nickel

CAS No. 7440-02-0

Reasonably anticipated to be a human carcinogen

First listed in the *First Annual Report on Carcinogens* (1980)

Also known as Ni

Carcinogenicity

Metallic nickel is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Metallic nickel caused tumors in two rodent species, at several different tissue sites, and by several different routes of exposure. In both rats and hamsters, metallic nickel powder caused tumors when administered by intratracheal instillation or by subcutaneous, intramuscular, or intraperitoneal injection. Intratracheal instillation of metallic nickel powder primarily caused adenocarcinoma, whereas injection most frequently caused sarcoma, demonstrating that metallic nickel can induce both epithelial and connective-tissue tumors (IARC 1973, 1976, 1990).

Cancer Studies in Humans

The available epidemiological studies of workers exposed to metallic nickel are limited by inadequate exposure information, low exposure levels, short follow-up periods, and small numbers of cases.

Nickel Compounds and Metallic Nickel

Studies on Mechanisms of Carcinogenesis

The available evidence suggests that metallic nickel has carcinogenic properties because it can slowly dissolve in the body and release ionic nickel, an active genotoxic and carcinogenic form of nickel. There is no evidence to suggest that the mechanisms by which nickel causes tumors in experimental animals would not also operate in humans.

Many studies in cultured rodent and human cells have shown that a variety of nickel compounds, including both soluble and insoluble forms of nickel, caused genetic damage, including DNA strand breaks, mutations, chromosomal damage, cell transformation, and disrupted DNA repair. Chromosomal aberrations have been observed in humans occupationally exposed to nickel. Nickel can bind ionically to cellular components, including DNA. The reduction-oxidation activity of the nickel ion may produce reactive oxygen species that attack DNA, and exposure to nickel ion *in vitro* or *in vivo* can result in production of 8-hydroxy-2'-deoxyguanosine in target tissues for cancer caused by nickel (IARC 1990, Kasprzak *et al.* 1990).

The carcinogenic potency of various nickel compounds varies widely, based on solubility properties and speciation. Studies indicate that soluble nickel salts can be complete carcinogens (Diwan *et al.* 1992) or initiators of carcinogenesis (Kasprzak *et al.* 1990) at tissue sites distant from the site of administration, which confirms that ionic nickel is the carcinogenic species. Differences in the potency of nickel compounds may relate to the specific properties of the compounds that affect the availability of ionic nickel at target sites. The listings of nickel compounds and metallic nickel are based on a large body of scientific evidence supporting the concept that nickel ion is carcinogenic. The hazard associated with a particular nickel compound is related largely to the compound's propensity to release ionic nickel in the body. The evidence suggests that the relatively insoluble metallic nickel is less likely to present a carcinogenic hazard than are the nickel compounds that tend to release proportionately more nickel ion. This view agrees with that expressed by IARC (1990), which based its evaluation of the carcinogenicity of nickel compounds as a group on the combined results of human epidemiological studies, cancer studies in experimental animals, and other data supporting the "underlying concept that nickel compounds can generate nickel ions at critical sites in their target cells." The IARC review noted that the carcinogenicity of nickel compounds depends not solely on their capacity to release ionic nickel, but also on factors that promote localization of high concentrations of nickel ions at critical tissue sites. This conclusion is consistent with evidence from studies in experimental animals indicating that nickel compounds of moderate solubility can,

under certain exposure conditions, be more carcinogenic than more soluble compounds. Therefore, it is difficult to predict with any certainty the relative carcinogenic hazard posed by a particular nickel compound without a full understanding of its ability to release ionic nickel under specific exposure conditions.

Properties

Metallic nickel is a group 10 metallic element. It is a lustrous, silvery, hard ferromagnetic metal or a gray powder. It has a vapor pressure of 1 mm Hg at 1,810°C. Metallic nickel is insoluble in water and ammonia, slightly soluble in hydrochloric acid and sulfuric acid, and soluble in dilute nitric acid. It is resistant to attack by air and water at standard temperatures. However, powdered nickel is reactive in air and may ignite spontaneously (IARC 1990, ATSDR 1997, HSDB 2009).

Nickel oxides and hydroxides are practically insoluble in water and soluble in acids and ammonium hydroxide. Nickel monoxide (also known as nickel oxide) is a green to black powder that becomes yellow when heated. The temperature at which the crystal is formed determines the color of the crystal. It is soluble in acids and ammonium hydroxide. Nickel monoxide reacts with acids to form nickel salts and soaps, and mixtures of nickel monoxide and barium oxide react violently with iodine and hydrogen sulfide in air. Nickel hydroxide occurs either as green crystals or as a black powder. It does not burn, but it may produce toxic gases when heated to decomposition. It is available at 97% purity (IARC 1990, HSDB 2009).

Nickel sulfides are insoluble in water, and some occur in more than one form. Nickel subsulfide (α form) occurs as lustrous pale-yellowish or bronze crystals that are soluble in nitric acid. Nickel sulfide occurs in three forms (α , β , and amorphous) as dark-green to black crystals or powder. Nickel disulfide occurs as black crystals or powder and decomposes at temperatures above 400°C (IARC 1990).

Nickel salts are green to yellow crystals that generally are soluble in water and decompose when heated. Nickel acetate occurs as a dull-green powder that effloresces somewhat in air. It is available as the tetrahydrate at greater than 97% purity. Nickel chloride occurs as yellow (anhydrous) or green (hexahydrate) deliquescent crystals. It is soluble in ethanol and ammonium hydroxide and insoluble in ammonia. The hexahydrate form is available as a laboratory reagent at greater than 99% purity or as industrial products containing approximately 24.7% nickel. Nickel sulfate occurs as yellow, green, or blue crystals and is available in anhydrous, hexahydrate, or heptahydrate forms. The hexahydrate melts at 53.3°C and the heptahydrate at 99°C; both forms are available at greater than 99% purity. Nickel carbonate occurs as light-green rhombic crystals. It is practically insoluble in water but soluble in dilute acids and ammonia. Laboratory reagent grades contain 45% or 47.5% nickel, and industrial grades contain approximately 45% nickel (IARC 1990, HSDB 2009).

Nickel carbonyl occurs as a colorless, volatile, highly flammable liquid with a musty odor. It is practically insoluble in water but soluble in alcohol, benzene, chloroform, acetone, and carbon tetrachloride, and insoluble in dilute acids and dilute alkalis. It is available in a technical grade at greater than 99% purity. Nickel carbonyl decays spontaneously in air and may decompose violently when exposed to heat or flame in the presence of air or oxygen. When heated or on contact with acid or acid fumes, it emits toxic carbon monoxide fumes (HSDB 2009). Nickelocene occurs as dark-green crystals. It is insoluble in water but soluble in common organic solvents. It is highly reactive and decomposes in air, acetone, alcohol, and ether. It is available in solid form at greater than 90% purity or as an 8% to 10% solution in toluene (IARC 1990).

Physical and chemical properties of metallic nickel and selected nickel compounds are listed in the table below, along with their chemical formulas.

Use

Because of its unique properties, nickel has many uses in industry. The majority (about 80%) of all nickel is used in alloys, because it imparts such properties as corrosion resistance, heat resistance, hardness, and strength (ATSDR 1997). The main uses of nickel are in the production of stainless steel, copper-nickel alloys, and other corrosion-resistant alloys. Pure nickel metal is used in electroplating, as a chemical catalyst, and in the manufacture of alkaline batteries, coins, welding products, magnets, electrical contacts and electrodes, spark plugs, machinery parts, and surgical and dental prostheses (IARC 1990, HSDB 2009). In 2009, 45% of the nickel used in the United States was used in stainless and alloy steel production, 39% in nonferrous alloys and superalloys, 11% in electroplating, and 5% in other uses. The end uses in 2009 were 32% in transportation, 14% in the chemical industry, 10% in electrical equipment, 8% in construction, 8% in fabricated metal products, 8% in the petroleum industry, 6% in household appliances, 6% in machinery, and 8% for other uses (Kuck 2010).

Nickel oxide sinters (a coarse form of nickel monoxide) are used in steel and alloy manufacturing. Green nickel monoxide is used in electronics, in fuel-cell electrodes, as a colorant in ceramics and glass, and to make nickel catalysts. Black nickel monoxide is used in the ceramics industry, to manufacture nickel catalysts, and to manufacture nickel salts. Nickel hydroxide is used in nickel-cadmium batteries and as a catalyst intermediate. Nickel sulfides are used as catalysts in the petrochemical industry when high concentrations of sulfur are present in the distillates and as intermediates in hydrometallurgical processing of silicate-oxide nickel ores (IARC 1990). Nickel subsulfide is used in lithium batteries (HSDB 2009).

Nickel salts are widely used in industry. Nickel acetate is used as a catalyst intermediate, as a dye fixative in the textile industry, in electroplating, and as a sealer for anodized aluminum. Nickel chloride is used in nickel catalysts, to absorb ammonia in industrial gas masks, and in electroplating. Nickel sulfates are used in electroplating and electrodeless nickel plating, as chemical intermediates to produce other nickel compounds, and in nickel flashings on steel to prepare it to be porcelain-enameled. Nickel carbonate is used to prepare nickel monoxide, nickel powder, nickel catalysts, colored glass, and certain nickel pigments. It also is used in electroplating and as a catalyst to remove organic contaminants from water (IARC 1990, HSDB 2009).

Nickel carbonyl is used in the production of high-purity nickel powder by the Mond process and for continuous nickel coatings on steel and other metals. It also has many small-scale applications, such as vapor plating of nickel and deposition of nickel in semiconductor manufacturing. Nickelocene is used as a catalyst and complexing agent (IARC 1990).

Production

Nickel is refined from either sulfide or silicate-oxide ores, which generally contain no more than 3% nickel. Magmatic sulfide ores are mined underground or by open-pit methods. Pentlandite ($[(\text{NiFe})_9\text{S}_8]$) is the principal sulfide ore; the largest known deposit is in Ontario, Canada, and substantial deposits are found in Minnesota, South Africa, Russia, Finland, and western Australia. Silicate-oxide ores, or garnierites, originate in (current or former) humid tropical regions and are surface mined by open-pit methods (IARC 1990, ATSDR 1997). Primary nickel production from mines in the United States was steady from the late 1950s to 1980, ranging from 10,000 to 14,000 metric tons (22 million to 31 million pounds) per year (USGS 2010). After 1980, primary production of nickel in the United States started declining, and no primary production has occurred since 1998, when 4,290 metric tons (9.5 million pounds) was produced.

Recycled scrap metal accounts for a large part of the nickel supply; in addition, relatively small quantities of nickel are recovered as a by-product at copper and precious-metal refineries or from reclamation of spent catalysts (Kuck 2009). Production from these secondary sources increased steadily from 21,000 metric tons (46 million pounds) in 1970 to a high of 106,000 metric tons (234 million pounds) in 2006, then declined to 63,500 metric tons (140 million pounds) in 2009.

From 1980 to 2008, U.S. consumption of nickel ranged from 163,000 to 250,000 metric tons (359 to 551 million pounds); consumption was highest in 2006 (USGS 2010). In 2009, consumption was 152,000 metric tons (335 million pounds), the lowest level since 1972 (Kuck 2010, USGS 2010). The demand for nickel is expected to grow because of increased demand for nickel-based batteries and nickel-bearing superalloys used in aircraft engines (Kuck 2009), with the United States being dependent on foreign sources for most nickel supplies.

From 1980 to 2008, U.S. imports of nickel remained fairly steady, ranging from 117,000 to 190,000 metric tons (258 million to 419 million pounds); 149,000 metric tons (329 million pounds) was imported in 2008. In 2009, imports fell to 114,800 metric tons (253 million pounds). U.S. exports of nickel ranged from 17,700 to 67,300 metric tons (39 to 148 million pounds) between 1980 and 2006, increasing to 116,000 metric tons (256 million pounds) in 2007, and were 99,680 metric tons (220 million pounds) in 2009 (Kuck 2010, USGS 2010).

Exposure

Environmental exposure to nickel occurs through inhalation, ingestion, and dermal contact. The general population is exposed to low levels of nickel because it is widely present in air, water, food, and consumer products. The general population takes in most nickel through food; the average daily intake from food in the United States is estimated at 150 to 168 μg . Typical daily intake from drinking water is 2 μg and from air is 0.1 to 1 μg . The general population is also ex-

Substance	Formula	Atomic or molec. wt.	Specific gravity	Melting point	Boiling point
Metallic nickel	Ni	58.7	8.91	1,455°C	2,730°C
Nickel monoxide	NiO	74.7	6.72	1,955°C	NR
Nickel hydroxide	Ni(OH) ₂	92.7	4.1	230°C (dec)	N/A
Nickel acetate	Ni(C ₂ H ₃ O ₂) ₂	176.8	1.80	NR	16.6°C
Nickel chloride	NiCl ₂	129.6	3.51	1,001°C	973°C (sub)
Nickel sulfate	NiSO ₄	154.8	4.01	848°C (dec)	N/A
Nickel carbonate	NiCO ₃	118.7	4.39	dec	N/A
Nickel carbonyl	Ni(CO) ₄	170.7	1.32	-19°C	43°C

Source: HSDB 2009. NR = not reported; dec = decomposes; N/A = not applicable; sub = sublimes.

posed to nickel in nickel alloys and nickel-plated materials, such as coins, steel, and jewelry, and residual nickel may be found in soaps, fats, and oils (ATSDR 1997).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, releases of nickel to the environment trended downwards from 1988 to 2003 and then increased, while releases of nickel compounds increased until 1998 but have since decreased by half. In 2007, 1,552 facilities released 8.3 million pounds of nickel, and 1,027 facilities released 30.5 million pounds of nickel compounds (TRI 2009).

Occupational exposure to nickel occurs mainly through inhalation of dust particles and fumes or through dermal contact. Nickel workers can also ingest nickel-containing dusts. Occupational exposure is common for workers involved in mining, smelting, welding, casting, spray-painting and grinding, electroplating, production and use of nickel catalysts, polishing of nickel-containing alloys, and other jobs where nickel and nickel compounds are produced or used (HSDB 2009). The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 23,272 workers potentially were exposed to nickel and nickel compounds (NIOSH 1976), and the National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 507,681 workers, including 19,673 women, potentially were exposed to nickel (molecular formula unknown) (NIOSH 1990).

Regulations

Department of Transportation (DOT)

Nickel carbonyl, nickel cyanide, nickel nitrate, and nickel nitrite are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials; nickel picrate is forbidden from transport.

Nickel carbonyl, nickel cyanide, and nickel tetracarbonyl are considered marine pollutants and special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Clean Air Act

Mobile Source Air Toxics: Nickel compounds are listed as mobile-source air toxics for which regulations are to be developed.

National Emissions Standards for Hazardous Air Pollutants: Nickel and its compounds are listed as hazardous air pollutants.

Prevention of Accidental Release: Threshold quantity (TQ) = 1,000 lb for nickel carbonyl.

Urban Air Toxics Strategy: Nickel compounds are identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Biosolids Rule: Limits have been established for nickel in biosolids (sewage sludge) when used or disposed of via land application, surface disposal, or incineration.

Effluent Guidelines: Nickel and nickel compounds are listed as toxic pollutants.

Water Quality Criteria: Based on fish or shellfish and water consumption = 610 µg/L for metallic nickel; based on fish or shellfish consumption only = 4,600 µg/L for metallic nickel.

Numerous nickel compounds are designated as hazardous substances.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb for nickel, nickel ammonium sulfate, nickel chloride, nickel nitrate, and nickel sulfate; 10 lb for nickel carbonyl, nickel cyanide, and nickel hydroxide.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Nickel and nickel compounds are listed substances subject to reporting requirements.

Threshold planning quantity (TPQ) = 1 lb for nickel carbonyl.

Reportable quantity (RQ) = 10 lb for nickel carbonyl.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of nickel or nickel compounds = P073, P074, F006.

Nickel and nickel compounds are listed as hazardous constituents of waste.

Food and Drug Administration (FDA)

Maximum permissible level of nickel in bottled water = 0.1 mg/L.

The color additives ferric ammonium ferrocyanide and ferric ferrocyanide, when used in drugs, may contain nickel at levels no greater than 200 ppm.

Menhaden oil may contain nickel at concentrations not to exceed 0.5 ppm.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 1 mg/m³ for elemental nickel and compounds other than nickel carbonyl; = 0.001 ppm (0.007 mg/m³) for nickel carbonyl.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value - time-weighted average (TLV-TWA) = 1.5 mg/m³ for elemental nickel; = 0.1 mg/m³ for soluble inorganic nickel compounds and nickel subsulfide; = 0.2 mg/m³ for insoluble inorganic nickel compounds; = 0.05 ppm for nickel carbonyl.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 0.015 mg/m³ for elemental nickel and nickel compounds other than nickel carbonyl; = 0.001 ppm (0.007 mg/m³) for nickel carbonyl.

Immediately dangerous to life and health (IDLH) limit = 10 mg/m³ for elemental nickel and nickel compounds other than nickel carbonyl; = 2 ppm [14 mg/m³] for nickel carbonyl.

Metallic nickel and nickel compounds are listed as potential occupational carcinogens.

References

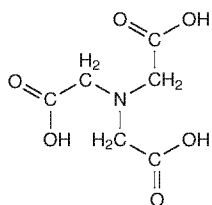
- Andersen A, Berge SR, Engeland A, Norseth T. 1996. Exposure to nickel compounds and smoking in relation to incidence of lung and nasal cancer among nickel refinery workers. *Occup Environ Med* 53(10): 708-713.
- ATSDR. 1997. *Toxicological Profile for Nickel*. Agency for Toxic Substances and Disease Registry. <http://www.atsdr.cdc.gov/toxprofiles/tp15.pdf>. 293 pp.
- Diwan BA, Kasprzak KS, Rice JM. 1992. Transplacental carcinogenic effects of nickel(II) acetate in the renal cortex, renal pelvis and adenohypophysis in F344/NCr rats. *Carcinogenesis* 13(8): 1351-1357.
- HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number. Last accessed: 10/22/09
- IARC. 1973. Nickel and inorganic nickel compounds. In: *Some Inorganic and Organometallic Compounds. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans*, vol. 2. Lyon, France: International Agency for Research on Cancer. pp. 126-149.
- IARC. 1976. Nickel and nickel compounds. In: *Cadmium, Nickel, Some Epoxides, Miscellaneous Industrial Chemicals and General Considerations on Volatile Anaesthetics. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans*, vol. 11. Lyon, France: International Agency for Research on Cancer. pp. 75-112.
- IARC. 1990. Nickel and nickel compounds. In *Chromium, Nickel and Welding. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans*, vol. 49. Lyon, France: International Agency for Research on Cancer. pp. 257-445.
- Kasprzak KS, Diwan BA, Konishi N, Misra M, Rice JM. 1990. Initiation by nickel acetate and promotion by sodium barbital of renal cortical epithelial tumors in male F344 rats. *Carcinogenesis* 11(4): 647-652.
- Kuck PH. 2009. *2007 Minerals Yearbook: Nickel [Advance Release]*. U.S. Geological Survey. <http://minerals.usgs.gov/minerals/pubs/commodity/nickel/myb1-2007-nicke.pdf>.
- Kuck, PH. 2010. Nickel. In *Mineral Commodity Summaries*. U.S. Geological Survey. <http://minerals.usgs.gov/minerals/pubs/commodity/nickel/mcs-2010-nicke.pdf>.
- NIOSH. 1976. *National Occupational Hazard Survey (1972-74)*. DHEW (NIOSH) Publication No. 78-114. Cincinnati, OH: National Institute for Occupational Safety and Health.
- NIOSH. 1990. *National Occupational Exposure Survey (1981-83)*. National Institute for Occupational Safety and Health. Last updated: 7/1/90. <http://www.cdc.gov/noes/noes1/50420sic.html>.
- NTP. 1996a. *Toxicology and Carcinogenesis Studies of Nickel Oxide (CAS No. 1313-99-1) in F344 Rats and B6C3F₁ Mice (Inhalation Studies)*. Technical Report Series no. 451. Research Triangle Park, NC: National Toxicology Program. 381 pp.
- NTP. 1996b. *Toxicology and Carcinogenesis Studies of Nickel Subsulfide (CAS No. 12035-72-2) in F344 Rats and B6C3F₁ Mice (Inhalation Studies)*. Technical Report Series no. 453. Research Triangle Park, NC: National Toxicology Program. 365 pp.
- TRI. 2009. *TRI Explorer Chemical Report*. U.S. Environmental Protection Agency. Last updated: 5/14/08. <http://www.epa.gov/triexplorer> and select Nickel.
- USGS. 2010. Nickel statistics. In *Historical Statistics for Mineral and Material Commodities in the United States*. Last updated 1/8/10. U.S. Geological Survey. <http://minerals.usgs.gov/ds/2005/140/nickel.pdf>.

Nitrilotriacetic Acid

CAS No. 139-13-9

Reasonably anticipated to be a human carcinogen

First listed in the *Third Annual Report on Carcinogens* (1983)



Carcinogenicity

Nitrilotriacetic acid is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to nitrilotriacetic acid caused urinary-tract tumors in mice and rats. Mice and rats of both sexes were administered nitrilotriacetic acid in the diet, both as the free acid and as the trisodium salt, and male rats were administered the trisodium salt in drinking water. These exposures increased the incidences of benign or malignant tumors of the kidney, ureter, and urinary bladder; tumor types observed included tubular-cell adenoma and adenocarcinoma of the kidney and transitional-cell carcinoma of the kidney, ureter, and urinary bladder. Exposure to the free acid caused benign and/or malignant kidney tumors in mice of both sexes and in male rats, cancer of the ureter in male rats, and cancer of the urinary-bladder in female rats. Exposure to the trisodium salt had the same effects in rats and also caused kidney tumors and cancer of the ureter in female rats (NCI 1977, Goyer *et al.* 1981).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to nitrilotriacetic acid.

Properties

Nitrilotriacetic acid is a tertiary amino-polycarboxylic acid chelating agent that exists as a white crystalline powder at room temperature (HSDB 2009, NCI 1977). It is slightly soluble in water and deuterated dimethyl sulfoxide, soluble in ethanol, and insoluble in most other organic solvents. It forms water-soluble complexes with many metals and reacts with strong oxidizing compounds (IARC 1990). Physical and chemical properties of nitrilotriacetic acid are listed in the following table.

Property	Information
Molecular weight	191.1 ^a
Specific gravity	> 1 at 20°C (solid) ^a
Melting point	242°C decomposes ^a
Log <i>K</i> _{ow}	-3.81 ^b
Water solubility	59 g/L at 25°C ^a
Vapor pressure	7 × 10 ⁻⁹ mm Hg at 25°C ^b
Dissociation constant (p <i>K</i> _a)	3.03 at 20°C ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Nitrilotriacetic acid has many commercial applications, but is used primarily as a metal ion chelating agent and as a laundry detergent builder (IARC 1990). It sequesters magnesium and calcium ions present in hard water, thereby reducing buildup and scaling caused by salts of these ions. In the late 1960s, nitrilotriacetic acid generally replaced phosphates in commercial detergents (NCI 1977). The use of nitrilotriacetic acid in detergents was suspended in the United States in 1971, but was resumed in the 1980s after phosphates were banned from detergents (HSDB 2009). Nitrilotriacetic acid also is used as an eluting agent in the purification of rare-earth elements, as a boiler feed water additive, in water and textile treatment, in metal plating and cleaning, and in pulp and paper processing (NCI 1977, IARC 1990). To a lesser extent, it is used in leather tanning, photographic development, synthetic rubber production, pharmaceutical manufacturing, and agricultural herbicide formulations and micronutrient solutions (NCI 1977). It has also been evaluated as a soil additive in the phytoremediation of heavy-metal-contaminated soil (Evangelou *et al.* 2007); chelation of the metals with nitrilotriacetic acid mobilizes them for more rapid uptake by plants.

Production

Nitrilotriacetic acid was first synthesized in 1862, and commercial production began in Europe in the 1930s (IARC 1990). In 1970, before its use in detergents was suspended, 150 million pounds of nitrilotriacetic acid was produced and used in the United States, of which 86% to 92% was used in detergents (NCI 1977). In the early 1980s, most of the annual U.S. production (approximately 66 million pounds) was exported (IARC 1990). In 2009, nitrilotriacetic acid was produced by 17 manufacturers worldwide, but none in the United States (SRI 2009), and was available from 31 suppliers, including 13 U.S. suppliers (ChemSources 2009). No current data on U.S. imports or exports of nitrilotriacetic acid were found. Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of nitrilotriacetic acid totaled 500,000 lb to 1 million pounds in 1986 and 1998, 1 million to 10 million pounds in 1990, and 10,000 to 500,000 lb in 1994 and 2000 (EPA 2004).

Exposure

The routes of potential human exposure to nitrilotriacetic acid are inhalation, ingestion, and dermal contact (HSDB 2009). The general population may be exposed through ingestion of drinking water or dermal contact with products containing nitrilotriacetic acid or its salts. Assessments of exposure to nitrilotriacetic acid were conducted in the United States in 1979, 1980, and 1985 and in Canada in 1996. These surveys assessed exposure from drinking water, bathing, wearing clothing washed with detergents containing nitrilotriacetic acid, contacting wash water, and ingesting residues remaining on hand-washed dishes. All of these studies concluded that the total daily exposure to consumers from all sources was less than 1 µg/kg of body weight per day (IARC 1999).

In 1988, EPA's Toxics Release Inventory reported environmental releases of 13,000 lb of nitrilotriacetic acid, of which 20% was released to air, 40% to surface water, and 40% to on-site landfills (TRI 2009). From 1988 to 1996, annual releases declined to a low of 1,600 lb. Since 1999, releases have ranged from 2,900 lb in 2000 to almost 64,000 lb in 2007, released by four industrial facilities. Most of the 2007 releases were to landfills, but almost 2,500 lb was released to an underground injection well.

When released to air, nitrilotriacetic acid will exist mostly in particulate form and will be removed by wet and dry deposition (HSDB

2009). In surface water, it will not volatilize or bioaccumulate in aquatic organisms; it will exist in ionized form and will likely remain in the water until biodegradation occurs, with a half-life of 0.34 to 15 days. Mean concentrations of nitrilotriacetic acid in surface water ranged from less than 0.5 to 6.4 mg/L in German rivers and lakes (Schmidt *et al.* 2004). In Canada, typical concentrations in ground and drinking water were 1 to 5 µg/L, and concentrations in Canadian environmental water samples ranged from 0.006 to 3.2 mg/L (Rak-sit 2002). In Canada and Switzerland, nitrilotriacetic acid makes up about 15% of laundry detergents; the load in raw wastewater was measured at 2,500 µg/L in Canada and 100 to 1,000 µg/L in Switzerland (Bucheli-Witschel and Egli 2001). In well-adapted activated sludge systems, nitrilotriacetic acid is readily biodegraded. In soil, it is likely to biodegrade under aerobic conditions and moderate temperatures (HSDB 2009).

Occupational exposure to nitrilotriacetic acid may occur through inhalation and dermal contact during the manufacture of the compound or its salts, during water treatment, and during other procedures in which nitrilotriacetic acid is used. The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 13,454 workers potentially were exposed to nitrilotriacetic acid, trisodium salt (NIOSH 1976). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 25,216 workers potentially were exposed to nitrilotriacetic acid and 249,479 workers potentially were exposed to its trisodium salt (NIOSH 1990). In 1990, it was estimated that approximately 2,600 workers potentially were exposed to nitrilotriacetic acid salts during production and detergent formulation; the potential for exposure was highest for workers loading hopper cars (IARC 1990).

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

References

- Bucheli-Witschel M, Egli T. 2001. Environmental fate and microbial degradation of aminopolycarboxylic acids. *FEMS Microbiol Rev* 25(1): 69-106.
- ChemIDplus. 2009. *ChemIDplus Advanced*. National Library of Medicine. <http://chem.sis.nlm.nih.gov/chemidplus/chemidheavy.jsp> and select Registry Number and search on CAS number. Last accessed: 2/19/09.
- ChemSources. 2009. *Chem Sources - Chemical Search*. Chemical Sources International. <http://www.chemsources.com/chemonline.html> and search on nitrilotriacetic acid. Last accessed: 2/24/09.
- EPA. 2004. *Non-confidential IUR Production Volume Information*. U.S. Environmental Protection Agency. <http://www.epa.gov/oppt/iur/tools/data/2002-vol.html> and search on CAS number. Last accessed: 4/21/05.
- Evangelou MWH, Ebel M, Schaeffer A. 2007. Chelate assisted phytoextraction of heavy metals from soil. Effect, mechanism, toxicity, and fate of chelating agents. *Chemosphere* 68(6): 989-1003.
- Goyer RA, Falk HL, Hogan M. 1981. Renal tumors in rats given trisodium nitrilotriacetic acid in drinking water for 2 years. *J Natl Cancer Inst* 66(5): 869-880.
- HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number. Last accessed: 2/24/09.
- IARC. 1990. Nitrilotriacetic acid and its salts. In *Some Flame Retardants and Textile Chemicals and Exposures in the Textile Manufacturing Industry*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 48. Lyon, France: International Agency for Research on Cancer. pp. 181-212.
- IARC. 1999. Nitrilotriacetic acid and its salts. In *Some Chemicals That Cause Tumors of the Kidney or Urinary Bladder in Rodents and Some Other Substances*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 73. Lyon, France: International Agency for Research on Cancer. pp. 385-399.
- NCI. 1977. *Bioassays of Nitrilotriacetic Acid (NTA) and Nitrilotriacetic acid, Trisodium Salt, Monohydrate (Na₃NTA·H₂O) for Possible Carcinogenicity* (CAS No. 139-13-9 [NTA], CAS No. 18662-53-8 [Na₃NTA·H₂O]). Technical Report Series No. 6, DHEW Pub. No. (NIH) 77-806. Bethesda, MD: National Cancer Institute. 185 pp.
- NIOSH. 1976. *National Occupational Hazard Survey (1972-74)*. DHEW (NIOSH) Publication No. 78-114. Cincinnati, OH: National Institute for Occupational Safety and Health.

NIOSH. 1990. *National Occupational Exposure Survey (1981-83)*. National Institute for Occupational Safety and Health. Last updated 7/1/90. <http://www.cdc.gov/noes/noes1/80058sic.html>, <http://www.cdc.gov/noes/noes1/m0951sic.html>, <http://www.cdc.gov/noes/noes1/x9062sic.html>.

Raksit A. 2002. Gas chromatographic and mass spectrometric analysis of nitrilotriacetic acid in environmental aqueous samples. *JAOAC Int* 85(1): 50-55.

Schmidt CK, Fleig M, Sacher F, Brauch HJ. 2004. Occurrence of aminopolycarboxylates in the aquatic environment of Germany. *Environ Pollut* 131(1): 107-124.

SRI. 2009. *Directory of Chemical Producers*. Menlo Park, CA: SRI Consulting. Database edition. Last accessed: 6/2/09.

TRI. 2009. *TRI Explorer Chemical Report*. U.S. Environmental Protection Agency. <http://www.epa.gov/triexplorer> and select Nitrilotriacetic Acid. Last accessed: 6/2/09.

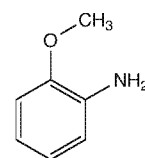
o-Nitroanisole

CAS No. 91-23-6

Reasonably anticipated to be a human carcinogen

First listed in the *Eighth Report on Carcinogens* (1998)

Also known as 2-nitroanisole



Carcinogenicity

o-Nitroanisole is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to *o*-nitroanisole caused tumors in two rodent species and at several different tissue sites. In rats of both sexes, dietary administration of *o*-nitroanisole caused mononuclear-cell leukemia and increased the combined incidences of benign and malignant tumors of the urinary bladder, kidney, and large intestine (NTP 1993, IARC 1996). In mice, it caused benign and malignant liver tumors (hepatocellular adenoma and carcinoma and hepatoblastoma) in males and benign liver tumors (hepatocellular adenoma) in females (NTP 1993).

Studies on Mechanisms of Carcinogenesis

Orally administered *o*-nitroanisole is metabolized predominantly to *o*-nitrophenol, which is conjugated to sulfate or glucuronide and eliminated in the urine. Less than 1% of *o*-nitroanisole is metabolized to *o*-anisidine, which is listed in the Report on Carcinogens as *reasonably anticipated to be a human carcinogen*. Dietary administration of *o*-anisidine hydrochloride caused tumors of the urinary bladder (transitional-cell neoplasia) in mice and rats and the kidney (transitional-cell carcinoma of the renal pelvis) in rats. *o*-Nitroanisole causes genetic damage in a wide variety of bacterial and *in vitro* mammalian test systems (NTP 1993, IARC 1996).

Since *o*-nitroanisole was listed in the *Eighth Report on Carcinogens*, additional studies relevant to mechanisms of carcinogenesis have been identified. *In vitro*, *o*-nitroanisole is metabolized by *O*-demethylation to 2-nitrophenol, which is oxidized to 2,5-dihydroxynitrobenzene and 2,6-dihydroxynitrobenzene (Miksanova *et al.* 2004a,b, Stiborova *et al.* 2004, Dracinska *et al.* 2006). *o*-Nitroanisole is also metabolized by nitroreduction to the DNA-reactive products 2-anisidine and *N*-(2-methoxyphenyl)hydroxylamine. DNA adducts similar to those found *in vitro* were found in the urinary bladder, liver, kidney, and spleen of male rats following intraperitoneal injection with *o*-nitroanisole. There is no evidence to suggest that mecha-

nisms by which o-nitroanisole causes tumors in experimental animals would not also operate in humans.

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to o-nitroanisole.

Properties

o-Nitroanisole is a colorless to yellowish liquid at room temperature. It is slightly soluble in water and soluble in alcohol and ether. It is stable under normal temperatures and pressures but is explosively reactive with sodium hydroxide and zinc (Akron 2009, HSDB 2009). Physical and chemical properties of o-nitroanisole are listed in the following table.

Property	Information
Molecular weight	153.1 ^a
Specific gravity	1.254 at 20°C/4°C ^a
Melting point	9.4°C ^a
Boiling point	277°C ^a
Log <i>K</i> _{ow}	1.73 ^a
Water solubility	1.690 g/L at 30°C ^a
Vapor pressure	3.6 × 10 ⁻³ mm Hg at 25°C ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

o-Nitroanisole is used primarily as a precursor for o-anisidine, which is produced through direct nitroreduction (NTP 1993). o-Anisidine is used extensively in the synthesis of over 100 azo dyes, either directly after being converted to a diazonium salt or as a precursor for dianisidine, which is diazotized and coupled. o-Nitroanisole has also been used as an intermediate in pharmaceutical production (IARC 1996).

Production

o-Nitroanisole is produced by treatment of 2-chloronitrobenzene with sodium methoxide under heat and pressure. The product separates as an oil after dilution with water (IARC 1996). In 2009, o-nitroanisole was produced by two manufacturers in India (SRI 2009) and was available from 17 suppliers worldwide, including 9 U.S. suppliers (ChemSources 2009). U.S. imports of o-nitroanisole totaled over 700,000 lb in 1976 and 540,000 lb in 1978 (HSDB 2009). No more recent data on U.S. imports or exports of o-nitroanisole were found.

Exposure

The routes of potential human exposure to o-nitroanisole are dermal contact, ingestion, and inhalation. o-Nitroanisole may be released into the environment by dye and pharmaceutical manufacturing facilities through various waste streams (HSDB 2009). When released to air, o-nitroanisole will remain in the vapor phase and will be degraded by reactions with photochemically produced hydroxyl radicals, with an estimated half-life of 109 hours. When released to water, it may adsorb to sediments and suspended solids. Volatilization is very slow, with a half-life of 105 days in a model river and 772 days in a model pond. When released to soil, o-nitroanisole has moderate mobility. It is not expected to bioaccumulate in aquatic organisms. o-Nitroanisole has been identified in drinking water, but no concentrations have been reported. Occupational exposure is associated with the widespread use of o-nitroanisole in the manufacture of azo dyes (NTP 1993); however, no estimates of occupational exposure to o-nitroanisole were found.

Regulations

Department of Transportation (DOT)

o-Nitroanisole is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

New Source Performance Standards: Manufacture of o-nitroanisole is subject to certain provisions for the control of volatile organic compound emissions.

References

- Akron. 2009. *The Chemical Database*. The Department of Chemistry at the University of Akron. <http://ull.chemistry.uakron.edu/erd> and search on CAS number. Last accessed: 2/19/09.
- ChemIDplus. 2009. *ChemIDplus Advanced*. National Library of Medicine. <http://chem.sis.nlm.nih.gov/chemidplus/chemidheavy.jsp> and search on CAS number. Last accessed: 2/19/09.
- ChemSources. 2009. *Chem Sources - Chemical Search*. Chemical Sources International. <http://www.chemsources.com/chemonline.html> and search on nitroanisole. Last accessed: 2/19/09.
- Dracinska H, Miksanova M, Svobodova M, Smrcek S, Frei E, Schmeiser HH, Stiborova M. 2006. Oxidative detoxication of carcinogenic 2-nitroanisole by human, rat and rabbit cytochrome P450. *Neuro Endocrinol Lett* 27(Suppl 2): 9-13.
- HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number. Last accessed: 2/19/09.
- IARC. 1996. 2-Nitroanisole. In *Printing Processes and Printing Inks, Carbon Black and Some Nitro Compounds*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol 65. Lyon, France: International Agency for Research on Cancer. pp. 369-380.
- Miksanova M, Novak P, Frei E, Stiborova M. 2004a. Metabolism of carcinogenic 2-nitroanisole in rat, rabbit, porcine and human hepatic cytosol. *Collec Czech Chem Commun* 69(3): 589-602.
- Miksanova M, Sulc M, Rydlova H, Schmeiser HH, Frei E, Stiborova M. 2004b. Enzymes involved in the metabolism of the carcinogen 2-nitroanisole: evidence for its oxidative detoxication by human cytochromes P450. *Chem Res Toxicol* 17(5): 663-671.
- NTP. 1993. *Toxicology and Carcinogenesis Studies of o-Nitroanisole (CAS No. 91-23-6) in F344 Rats and B6C3F₁ Mice (Feed Studies)*. NTP Technical Report Series no. 416, NIH Publication no. 93-3147. Research Triangle Park, NC: National Toxicology Program. 482 pp.
- SRI. 2009. *Directory of Chemical Producers*. Menlo Park, CA: SRI Consulting. Database edition. Last accessed: 2/19/09.
- Stiborova M, Miksanova M, Smrcek S, Bieler CA, Breuer A, Klokow KA, Schmeiser HH, Frei E. 2004. Identification of a genotoxic mechanism for 2-nitroanisole carcinogenicity and of its carcinogenic potential for humans. *Carcinogenesis* 25(5): 833-840.

Nitroarenes (Selected)

Introduction

The nitroarenes are a large class of structurally related chemicals normally found in particulate emissions from many combustion sources, most notably, diesel exhausts. These molecules are nitro-substituted derivatives of polycyclic aromatic hydrocarbons (arenes) with at least one nitro group covalently bound to a cyclic carbon atom (i.e., nitro-polycyclic aromatic hydrocarbons, or nitro-PAHs) (Rosenkratz and Mermelstein 1985, Tokiwa and Ohnishi 1986). The nitroarenes result from incomplete combustion processes from sources such as kerosene heaters and fuel gas burners, in addition to diesel engines. Profiles for the following listed nitroarenes follow this introduction:

- 1,6-Dinitropyrene
- 1,8-Dinitropyrene
- 6-Nitrochrysene
- 1-Nitropyrene
- 4-Nitropyrene

Following are brief discussions of carcinogenicity and exposure for nitroarenes in general. Additional information on carcinogenicity and exposure specific to each of the five listed nitroarenes is provided in the individual profiles.

These nitroarene compounds were first listed in the *Eighth Report on Carcinogens* (1998) as *reasonably anticipated to be human carcinogens* based on evidence of carcinogenicity from studies in experimental animals. Few members of this large class of chemicals have

been rigorously evaluated in state-of-the-art cancer studies in rodents. Typically, the chemicals were administered by injection, over short periods, and with less-than-optimal time allowed for tumors to fully develop. Despite these limitations, the results of carcinogenicity studies of nitroarenes in animals were generally similar and demonstrated tumor formation both at the site of injection and at distant tissue sites. The mutagenic and carcinogenic properties of the nitroarene compounds vary. The mutagenicity of nitropyrenes in *Salmonella typhimurium* strains TA98 and TA98NR increased as the number of nitro groups increased (NTP 1999). The order of mutagenic potency in human cells, from most potent to least potent, was 1,6-dinitropyrene, followed by 1,8-dinitropyrene, followed by 1-nitropyrene (Durant 1996), and levels of DNA binding in the rat mammary gland were higher for 4-nitropyrene than for 1-nitropyrene (Chae *et al.* 1997).

The metabolic pathways for activation of these nitroarene molecules to create reaction products with the ability to cause gene mutations or changes in the structure of DNA have been described in tissues from humans and animals. The metabolic pathways are similar for the five listed nitroarenes. Two successive nitroreduction steps form an *N*-hydroxylamine group. This intermediate may be activated by loss of the *N*-hydroxyl group or by *O*-acetylation of the *N*-hydroxylamine group followed by removal of the acetate to form the DNA-reactive nitrenium ion, or it may be inactivated by further reduction to an amine. No adequate studies of the relationship between exposure to these chemicals and human cancer have been reported. However, exposure to diesel exhaust particulates is listed in the Report on Carcinogens as *reasonably anticipated to be a human carcinogen* based on findings of elevated lung-cancer rates in occupational groups exposed to diesel exhaust and on supporting studies of cancer in experimental animals and studies on mechanisms of carcinogenesis. Whether the nitroarenes are responsible for or contribute to the carcinogenicity of diesel exhaust in humans has not been determined.

Nitroarenes are products of incomplete combustion in the presence of nitrating species (IPCS 2003). They have been identified in extracts of particles from the exhaust of diesel engines (IARC 1989). Nitroarene concentrations measured in diesel-exhaust extracts were higher for heavy-duty engines during operation and lower for engines at idle (IARC 1989, Yamazaki *et al.* 2000). Nitroarenes have also been identified in particulate matter from the incineration of municipal waste, coal fly ash, extracts of coke-oven emissions, and stack emissions from a facility manufacturing carbon electrodes. Concentrations of nitroarenes in ambient air are higher in heavily industrialized areas than in nonindustrialized urban areas, suburban areas, or rural areas (IARC 1989) and vary seasonally and diurnally. Higher concentrations in winter reflect increased emissions from heating sources, and diurnal variations reflect traffic patterns (IPCS 2003).

Because nitroarenes emitted to air are tightly bound to particulate matter, they may be removed from the atmosphere by wet and dry deposition and deposited on soil or surface water by settling and by precipitation. In Japan, all five listed nitroarenes were detected in particulates derived from coal burning (Taga *et al.* 2005) and in precipitation (Murahashi *et al.* 2001). Nitroarenes have been found in the indoor environment in particulate emissions from kerosene heaters and gas burners used for home heating and cooking (IPCS 2003). Before 1980, considerable amounts of all five listed nitroarenes were found in samples of carbon black that was known to be used in photocopiers. Some nitroarene compounds have also been identified in food products, especially in smoked and grilled meats, and in beverages, especially tea (IARC 1989).

References

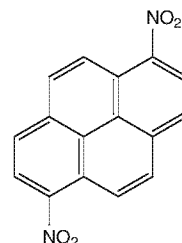
- Chae YH, Upadhyaya P, Ji BY, Fu PP, el-Bayoumy K. 1997. Comparative metabolism and DNA binding of 1-, 2-, and 4-nitropyrene in rats. *Mutat Res* 376(1-2):21-28.
- Durant JL, Busby WF Jr, Lafleur AL, Penman BW, Crespi CL. 1996. Human cell mutagenicity of oxygenated, nitrated and unsubstituted polycyclic aromatic hydrocarbons associated with urban aerosols. *Mutat Res* 371(3-4):123-157.
- IARC. 1989. 1,6-Dinitropyrene. In *Diesel and Gasoline Engine Exhausts and Some Nitroarenes*. IARC Monographs Evaluation of Carcinogenic Risks of Chemicals to Humans, vol. 46. Lyon, France: International Agency for Research on Cancer. pp. 215-230.
- IPCS. 2003. *Environmental Health Criteria No. 229. Selected Nitro- and Nitro-oxy-polycyclic Aromatic Hydrocarbons*. International Programme on Chemical Safety. <http://www.inchem.org/documents/ehc/ehc/ehc1229.htm>.
- Murahashi T, Ito M, Kizu R, Hayakawa K. 2001. Determination of nitroarenes in precipitation collected in Kanazawa, Japan. *Water Res* 35(14):3367-3372.
- NTP. 1999. *NTP Report on Carcinogens Background Document for 4-Nitropyrene*. National Toxicology Program. <http://ntp.niehs.nih.gov/files/Nitropyrene-4.pdf>. 19 pp.
- Rosenkranz H, Mermelstein R. 1985. The genotoxicity, metabolism and carcinogenicity of nitrated polycyclic aromatic hydrocarbons. *J Environ Sci Health C3*(2):221-272.
- Taga R, Tang N, Hattori T, Tamura K, Sakai S, Toriba A, Kizu R, Hayakawa K. 2005. Direct-acting mutagenicity of extracts of coal burning-derived particulates and contribution of nitropolycyclic aromatic hydrocarbons. *Mutat Res* 581(1-2):91-95.
- Tokiwa H, Ohnishi Y. 1986. Mutagenicity and carcinogenicity of nitroarenes and their sources in the environment. *Crit Rev Toxicol* 17(1):23-60.

1,6-Dinitropyrene

CAS No. 42397-64-8

Reasonably anticipated to be a human carcinogen

First listed in the *Eighth Report on Carcinogens* (1998)



Carcinogenicity

1,6-Dinitropyrene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

1,6-Dinitropyrene caused tumors in several rodent species, at several different tissue sites, and by several different routes of exposure. Subcutaneous injection of 1,6-dinitropyrene caused cancer at the injection site (sarcoma) in male mice and in rats of both sexes and leukemia in female rats (IARC 1989). Exposure by intraperitoneal injection caused benign and malignant liver tumors (adenoma and carcinoma) in male mice and cancer of the peritoneal cavity (sarcoma) in female rats (IARC 1989, Iizasa *et al.* 1993). Intrapulmonary instillation of 1,6-dinitropyrene caused lung cancer (squamous-cell carcinoma) in male rats (IARC 1989, Iwagawa *et al.* 1989), and intratracheal instillation caused lung cancer (adenocarcinoma) and myeloid leukemia in hamsters of both sexes (IARC 1989). Administration of 1,6-dinitropyrene to female rats by stomach tube caused cancer of the pituitary gland (carcinoma) (IARC 1989, Imaida *et al.* 1991).

Studies on Mechanisms of Carcinogenesis

Pathways of 1,6-dinitropyrene metabolism leading to mutagenic and clastogenic metabolites and formation of DNA adducts have been